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The Nutritional Status of Patients with Clostridium Difficile Associated Disease and Dietetic Practices Concerning the Management of These Patients

Yvonne Hickey

Dublin Institute of Technology

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The nutritional status of patients with *Clostridium difficile* associated disease and dietetic practices concerning the management of these patients

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BSc Human Nutrition and Dietetics (TCD); Graduate Diploma Human Nutrition and Dietetics (DIT)

A thesis submitted for the degree of Master of Philosophy

Dublin Institute of Technology

Supervisors:

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Dr Denise Drudy

School of Biological Sciences

June 2012
Abstract

Background: *Clostridium difficile* is a leading cause of nosocomial infection and is responsible for increased morbidity and mortality (Hookman & Barkin, 2009). There are limited data available on the nutritional status and dietetic management of these patients.

Aims:

1. To carry out an observational study to assess the prevalence of the risk of malnutrition in patients with *Clostridium difficile* associated disease (CDAD) and compare it to a group of patients in the same hospital.

2. To investigate dietitians’ beliefs and recommendations of probiotics in CDAD and determine the probiotic products and strains being used in this patient group. To assess the current enteral feeding practices of dietitians in patients with CDAD.

Methods: The Malnutrition Screening Tool (MUST) was used to assess the prevalence of risk of malnutrition in the patients with CDAD and a hospital comparison group. A questionnaire was sent to members of the Irish Nutrition and Dietetic Institute to gather information on dietitians’ opinions and use of probiotics and their enteral feeding practices in patients with CDAD.

Results: There was no significant difference in the prevalence of malnutrition risk (MUST of 1 or more) between the CDAD group (75.5%) compared to the hospital comparison group (66.7%). The questionnaire response rate was 41% with 215 questionnaires undergoing analysis. One-third (34.5%) of dietitians considered probiotics to have a role in the prevention of CDAD yet only 11% used them in
practice. Almost two-thirds (65.4%) believed that they have a role in the treatment of CDAD but only 40% regularly used them in practice. A yogurt drink containing *Lactobacillus rhamnosus* GG was mostly commonly available probiotic product for use by dietitians. When enterally feeding patients with CDAD, the majority of dietitians use a polymeric feed (79.6%).

Conclusion: Both patient groups studied were at similar nutritional risk. There are mixed beliefs among Irish dietitians on the role of probiotics in CDAD. Probiotics are frequently recommended by dietitians in their clinical practice with little standardisation in practice. The probiotic strain that is most commonly being used in patients with CDAD does not have strong evidence to support its use.
Declaration of Work

I certify that this thesis which I now submit for examination for the award of Master of Philosophy (MPhil), is entirely my own work and has not been taken from the work of others, save and to the extent that such work has been cited and acknowledged within the text of my work.

This thesis was prepared according to the regulations for postgraduate study by research of the Dublin Institute of Technology and has not been submitted in whole or in part for another award in any Institute.

The work reported on in this thesis conforms to the principles and requirements of the Institute’s guidelines for ethics in research.

The Institute has permission to keep, lend or copy this thesis in whole or in part, on condition that any such use of the material of the thesis be duly acknowledged.

Signature________________________________  Date___________________________

Candidate
Acknowledgements

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My appreciation is due to members of the INDI council and INDI members for their time and participation in the questionnaire. I would like to acknowledge the support of the dietetic department in St Vincent’s University Hospital for all their assistance and encouragement.

Finally I thank my family and friends for their constant support and interest.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAD</td>
<td>Antibiotic associated diarrhoea</td>
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<tr>
<td>ASPEN</td>
<td>American Society for Parenteral and Enteral Nutrition</td>
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<tr>
<td>BAPEN</td>
<td>British Society of Parenteral and Enteral Nutrition</td>
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<tr>
<td>BDA</td>
<td>British Dietetic Association</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>C. difficile</td>
<td>Clostridium difficile</td>
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<td>CDAD</td>
<td>Clostridium difficile associated disease</td>
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<tr>
<td>CFU</td>
<td>Colony forming units</td>
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<tr>
<td>CVC</td>
<td>Central venous catheter</td>
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<tr>
<td>DIT</td>
<td>Dublin Institute of Technology</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
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<tr>
<td>E. coli</td>
<td>Escherichia. coli</td>
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<tr>
<td>EFT</td>
<td>Enteral feeding tube</td>
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<tr>
<td>ESCMID</td>
<td>European Society of Clinical Microbiology and Infectious Diseases</td>
</tr>
<tr>
<td>ESPEN</td>
<td>European Society for Parenteral and Enteral Nutrition</td>
</tr>
<tr>
<td>FF</td>
<td>Functional Food</td>
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<tr>
<td>FOS</td>
<td>Fructo-oligosaccharides</td>
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<tr>
<td>FSAI</td>
<td>Food Safety Authority Ireland</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>g</td>
<td>Grammes</td>
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<tr>
<td>GIT</td>
<td>Gastrointestinal tract</td>
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<tr>
<td>GOS</td>
<td>Galacto-oligosaccharides</td>
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<tr>
<td>HPSC</td>
<td>Health Protection Surveillance Centre</td>
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<tr>
<td>HSE</td>
<td>Health Service Executive</td>
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<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
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<td>IBS</td>
<td>Irritable bowel syndrome</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>INDI</td>
<td>Irish Nutrition and Dietetic Institute</td>
</tr>
<tr>
<td>kg</td>
<td>Kilogrammes</td>
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<tr>
<td>L. rhamnosus GG</td>
<td><em>Lactobacillus rhamnosus GG</em></td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>mg</td>
<td>Milligrammes</td>
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<tr>
<td>MNA</td>
<td>Mini Nutritional Assessment</td>
</tr>
<tr>
<td>Mphil</td>
<td>Master of Philosophy</td>
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<tr>
<td>MUST</td>
<td>Malnutrition Universal Screening Tool</td>
</tr>
<tr>
<td>n</td>
<td>Sample size</td>
</tr>
<tr>
<td>NGT</td>
<td>Nasogastric tube</td>
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<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>NJT</td>
<td>Nasojejunal tube</td>
</tr>
<tr>
<td>NK</td>
<td>Natural killer</td>
</tr>
<tr>
<td>NRS</td>
<td>Nutrition risk score</td>
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<tr>
<td>NSW</td>
<td>Nutrition screening week</td>
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<tr>
<td>ONS</td>
<td>Oral nutrition supplements</td>
</tr>
<tr>
<td>PEG</td>
<td>Percutaneous endoscopic gastrostomy</td>
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<tr>
<td>PMC</td>
<td>Pseudomembraneous colitis</td>
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<tr>
<td>PN</td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>PPI’s</td>
<td>Proton pump inhibitors</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised control trial</td>
</tr>
<tr>
<td>ROI</td>
<td>Republic of Ireland</td>
</tr>
<tr>
<td>SCFA</td>
<td>Short chain fatty acid</td>
</tr>
<tr>
<td>SGA</td>
<td>Subjective global assessment</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
</tr>
<tr>
<td>SUVH</td>
<td>St Vincent’s University Hospital</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations International Children Emergency Fund</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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CHAPTER 1 - Literature Review
Part 1 - *Clostridium difficile* associated disease

1.1 *Clostridium difficile*

The human gastrointestinal tract (GIT) contains up to $10^{14}$ microorganisms comprised of around one thousand different bacterial species (Backhed *et al.*, 2005). Some of these microorganisms live permanently in the GIT while others are introduced with food or other contaminants and pass through the tract. The stomach contains very few resident bacteria due to its low pH. The upper intestine also contains small numbers of microorganisms due to the presence of bile salts and the action of peristalsis. A dramatic increase in the number and variety of microorganisms, in particular, anaerobes is found in the colon. One such anaerobe, estimated to form part of the faecal flora in approximately 3% of healthy adults, is the gram positive, spore-forming *Clostridium difficile* (*C. difficile*) (Viscidi *et al.*, 1981). The bacterium was first described in 1935 by Hall and O’Toole as part of the normal intestinal flora of newborn infants (Hall & O'Toole, 1935). The bacterium is present in over 20% of hospitalised patients (Starr, 2005) and has been identified in 4-20% of patients in long term care facilities (Simor *et al.*, 2002). It is a major cause of nosocomial infection, and has been associated with an increased incidence of morbidity and mortality, in hospitals and long term care facilities (Loo *et al.*, 2005; McDonald *et al.*, 2005; Pepin *et al.*, 2005a). In 1978, *C. difficile* was identified as the pathogen responsible for pseudomembranous colitis (PMC) (Bartlett *et al.*, 1978).

Acquisition of *C. difficile* occurs by oral ingestion of spores. These spores are resistant to the acidity of the stomach and germinate into the vegetative form in the alkaline environment of the small intestine. Disruption of the commensal flora of the colon, typically through exposure to antimicrobial medication, allows *C. difficile* to flourish and produce toxins. The two main exotoxins that are produced are toxin A
and toxin B, both of which are cytotoxic and enteropathic in the human intestine. Both toxins appear to have cytotoxic effects through disruption of the actin cytoskeleton within cells (Rupnik et al., 2005). The toxins loosen the junctions of the epithelial cells that line the colon allowing for penetration between epithelial cells (Starr, 2005). This begins the cascade of a tissue damaging inflammatory process that involves releasing destructive leukotrienes and cytokines, with the subsequent death of epithelial cells by apoptosis. The cytokines identified as being involved are interleukins (IL) 6, IL8, IL 1β, leukotriene B4 and interferon γ. Epithelial cells and monocytes have been found to be more sensitive to C. difficile toxin A induced death than lymphocytes (Mahida et al., 1996). More recently, a third toxin (binary toxin) encoded by the cdtA and cdtB genes has been found in 10% of strains (Goncalves et al., 2004). The role of this third toxin in disease development is still unclear (Pituch, 2009). It has been suggested that it has a clinically relevant role (Barbut et al., 2005). A correlation between the amount of toxin produced and the extent of clinical disease is not thought to exist (Akerlund et al., 2006).

1.2 Definition of Clostridium difficile associated disease (CDAD)
The Health Protection Surveillance Centre (HPSC) of Ireland has adopted the definition of CDAD recommended by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study group for C. difficile and the European Centre for Disease Prevention and Control (ECDC) (Kuijper et al., 2006). In Ireland, Clostridium difficile associated disease (CDAD) is diagnosed when patients have one or more of the following criteria: diarrhoeal stools or toxic megacolon with either a positive laboratory assay of C. difficile toxin A and/or toxin B in stools or a toxin producing C. difficile organism detected in stool culture or by other laboratory methods. PMC can only be diagnosed by endoscopy and/or colonic histopathology.
In all cases, diarrhoea is defined as three or more loose or watery bowel movements in a 24-hour period. Similar criteria are used to diagnose recurrent CDAD (Cohen et al., 2010). The infection is classified as severe when there is admission to an intensive care unit (ICU) for treatment of CDAD or its complications, surgery for toxic megacolon, perforation or refractory colitis or death within 30 days of diagnosis if CDAD is either the primary or a contributory cause. Admission to a healthcare facility for treatment of community associated CDAD is also classified as severe infection. According to the HPSC, CDAD can also be classified according to its origin as follows: “Health care associated” CDAD or “Community associated” CDAD. The HPSC classifies acquisition as “unknown” when CDAD presents in a patient who was discharged from a healthcare facility 4-12 weeks before the onset of symptoms (HPSC, 2008).

CDAD has been classified as recurrent if an episode of CDAD occurs within eight weeks following the onset of a previous episode, provided that the CDAD symptoms from the earlier episode resolved with or without therapy. Older age, low quality of life score and being female are known risk factors for disease recurrence (McFarland et al., 1999). Following a first episode of CDAD, 24% of patients relapse within two months (Sunenshine & McDonald, 2006). Having one recurrence of CDAD increases the risk of subsequent recurrences (McFarland et al., 1999). Re-infection with different strains of C. difficile has been found in a large proportion of recurrences (Barbut et al., 2000). The risk of recurring infection increases to 50-65% of patients with two or more previous episodes (Rohde et al., 2009).
1.3 Clinical manifestations of CDAD

The spectrum of *C. difficile* human disease ranges from asymptomatic colonisation to potentially fatal colitis. Fulminant, life threatening PMC is the extreme end of the spectrum of disease and occurs in 3-5% of those affected (Jobe *et al.*, 1995; Rubin *et al.*, 1995). The symptoms of CDAD usually begin soon after colonisation, with median time to onset of 2-3 days (McFarland *et al.*, 1989; Johnson *et al.*, 1990; Samore *et al.*, 1994; Kyne *et al.*, 2000). Typically, CDAD presents as diarrhoea, abdominal cramps, fever and leukocytosis occurring from several days to 10 weeks after antibiotic therapy (Kelly *et al.*, 1994; Kyne *et al.*, 1999; Bartlett *et al.*, 2002).

Histologically, the disease is characterized by focal epithelial ulceration associated with inflammatory exudates (Price & Davies, 1977). Severely ill patients may have no diarrhoea due to dilation of the colon (toxic megacolon) and paralytic ileus that may result from loss of colonic muscular tone (Kelly *et al.*, 1994; Kyne *et al.*, 1999; Bartlett *et al.*, 2002). In severely ill patients, with no response to treatment, a colectomy may be required (Bartlett, 2002). In general, complications of diarrhoea threaten the already compromised health and well being of the hospitalised patient. Severe diarrhoea can result in haemodynamic and metabolic instability due to fluid and electrolyte imbalance. Incontinence of diarrhoeal stool is a major cause of perianal skin damage. An unusual manifestation of CDAD was described by Dansinger *et al.*, (1996) who reported that up to half of patients with indolent *C. difficile* infection develop manifestations of protein losing enteropathy involving ascites, peripheral oedema and hypoalbuminaemia. Inflammation of the bowel may result in leakage of albumin across the lumen causing colonic loss of albumin with inadequate compensatory hepatic synthesis (Hookman & Barkin, 2009). Psychological problems are often overlooked, as diarrhoea can be exhausting and
embarrassing for the patient (Thorson et al., 2008). Complications result in extended hospital stay (on average by 3-7 days), an increase in unrelated infections and a two to three times increased risk of mortality (McFarland, 2006). Kuijper et al., (2006) have estimated the cost of CDAD to the healthcare system as between €5-15,000 per case in the United Kingdom. CDAD results in a total expenditure of $1.1 billion per year in the United States (Kuijper et al., 2006).

1.4 Immune response to CDAD
The host immune response to \textit{C. difficile} colonisation and toxin production is crucial in influencing disease severity, but not all patients have a similar immunological response (Jiang et al., 2007). The earliest research in this area reported an antibody response in 64% of adults to toxin A and in 66% of adults to toxin B. Antibody levels to toxin B were higher in the serum of convalescent CDAD patients when compared to those of a control population (Viscidi et al., 1983). Kyne et al., (2000) reported that asymptomatic carriage of \textit{C. difficile} was strongly associated with an immune response to \textit{C. difficile} toxins, and this was demonstrated by high serum levels of IgG antibody against toxin A.

1.5 Changing epidemiology of CDAD
In recent years, there has been an unexpected increase in CDAD infection with large outbreaks in North America and Europe (Kuijper et al., 2006). In many of the locations where the increase has been identified, the disease has become more serious and refractory to standard therapy. These recent outbreaks have been associated with the unique strain of \textit{C. difficile} that has been identified as B1/NAP1/027 or “ribotype 027”. This strain is now affecting relatively healthy adults, including some who have not been exposed to the hospital setting or recent antibiotics. B1/NAP1/027 strain is characterized as toxinotype III and has a 18-bp deletion within the tcdC gene
(putative negative regulator for the production of toxins A and B) as well as a deletion at position 117. It produces 23 and 16 times more toxin B and A respectively in vitro than previously described (Warny et al., 2005). This strain has a high resistance to fluoroquinolones (Pepin et al., 2005a) and the mortality associated with the new strain has been estimated to be between 6-12% (Pepin et al., 2005b; Smith, 2005; Paltansing et al., 2007).

An increased incidence of the disease has also been identified in the community setting; again affecting people who would traditionally have been at low risk (Wilcox et al., 2008). Mc Farland et al., (2007), observed patients with community-acquired CDAD were younger, had less severe disease and that most had no prior exposure to antibiotics. It has been suggested that this may be because CDAD is an emerging problem, or that possibly that the disease was overlooked in the past (Weese, 2010). A variety of hypotheses has been proposed to explain the current outbreaks of CDAD in the community. Levels of exposure to the organism and its spores may have increased due to the possible colonisation of recently discharged patients from hospitals, increased asymptomatic carriage and increased contact with asymptomatic carriers (Bauer et al., 2008a). Weese (2010) commented that animals and contaminated food may be a source of C. difficile, especially in community-associated CDAD.

### 1.6 CDAD in Ireland

Until recently there was limited information from the Republic of Ireland on CDAD. However, in May 2008, it became a notifiable disease. In 2009, there were 1897 new cases of CDAD reported (HPSC, 2009) and this decreased to 1696 new cases in 2010 (HPSC, 2010). In both years, the disease was more prevalent in females (59% in
2010) and in those over 65 years of age (HPSC, 2009; HPSC, 2010). Further information about the disease in Ireland was captured during a one month national enhanced surveillance in March 2009. Typing and antimicrobial susceptibility of 211 cases of *C. difficile* infection from 33 healthcare facilities was conducted. The results found that the majority of patients had been treated with antibiotics in the previous eight weeks prior to developing CDAD. 10% of the cases were community-associated and 83% were health-care associated. The most common ribotypes identified were 027, 106, 078, 044,014 and 001 (Fenelon *et al.*, 2009).

### 1.7 Risk factors for the development of CDAD

There are a number of identifiable risk factors known to increase the likelihood of colonisation and development of CDAD. The most common risk factors are exposure to antibiotics, advanced age and hospitalisation. Other factors which are attributed to increased risk are; recent gastrointestinal surgery or procedures, immunosuppressive therapy, severe underlying disease, use of enteral tube feeding (ETF) and proton pump inhibitors (PPIs) (Bignardi, 1998).

#### 1.7.1 Antibiotics

There are multifactorial mechanisms by which antibiotics lead to increased susceptibility to the acquisition of *C. difficile*. Antibiotics destabilise the GIT microflora and can alter the integrity of epithelial surfaces (Levy, 2000). In addition, they increase peristalsis by acting as colonic irritants. The extent to which they affect colonic microflora depends on the composition of the original microflora, the spectrum of activity and dosage of the antibiotic, the route and duration of administration and concentration of the active drug in the GIT. The most commonly reported antibiotics implicated in the development of CDAD are clindamycin, cephalosporins and fluoroquinolones (Bartlett, 1992). CDAD usually begins 4-9 days
after the antibiotic therapy has stopped but it can occur up to eight weeks post treatment (Rohde et al., 2009). Approximately 5-30% of patients receiving antibiotics, particularly broad spectrum antibiotics, develop diarrhoea either during the course of treatment or up to two months after the course finished (Hogenauer et al., 1998).

1.7.2 Hospitalisation and length of stay
The risk of developing CDAD is highly correlated with the length of hospital stay (Clabots et al., 1992). This is most likely due to the increased risk of exposure to spores while in hospital (Imhoff & Karpa, 2009). The hands of health care workers contaminated with C. difficile spores are the most probable vehicle for the spread of spores during non-outbreak periods (Fekety et al., 1981; McFarland et al., 1989). Spores of C. difficile are resistant to alcohol and standard hospital germicides (Wult et al., 2003a). To limit the spread of CDAD a number of infection control measure are required, these include; staff education, use of patient isolation, protective clothing, hand hygiene, environmental clean cleaning of medical equipment and good antibiotic stewardship (Vonberg et al., 2008).

1.7.3 Increasing age
Older age is considered a risk factor for the acquisition of C. difficile. A Swedish group reported that the rate of CDAD per 100,000 persons older than 65 years was 20 times higher than that in persons younger than 20 years of age (Karlstrom et al., 1998). Factors which are thought to be involved in the increased risk include age-related changes in faecal flora, immune system dysfunction or more severe underlying disease.
Studies have shown a decrease in the level of beneficial and protective bacteria in the GIT in later life, and an increase in species diversity (Woodmansey, 2007). There is a decrease in the number of bifidobacteria with increasing age (O’Connell, 2009). Bifidobacteria are capable of inhibiting the growth of many pathogenic bacterial species; and any reduction in the number of beneficial bacteria increases the risk of growth of pathogenic organisms. Such alterations in GIT microflora with age could result in a reduced functionality and immune responsiveness in the gut and increase susceptibility to infections (Woodmansey, 2007). Weakening of the immune system also occurs with increasing age, and this can increase susceptibility to infection. There is a reduction in the production of antibodies and T-cells. Natural killer (NK) cells may also be reduced in number and activity (Takeda & Okumura, 2007).

1.7.4 Intensive care setting
Being a patient in ICU is acknowledged to be an independent risk factor for the development of CDAD (Bignardi, 1998). Patients admitted to ICU are bed-bound, have more severe underlying disease and decreased bowel motility. They are generally mechanically ventilated, receiving narcotics and at risk of developing bowel ischemia. A decrease in bowel motility may allow those colonised with C. difficile to develop colitis by increasing the exposure time of the toxin to its receptor (Modena et al., 2005).

1.7.5 Proton pump inhibitors (PPIs)
Dial et al., (2007) estimated that the increased risk of developing CDAD with current use of PPIs is 2.9 (95% CI 1.6-3.4). Gastric acid production is a key host defence mechanism. PPIs inhibit an individual’s defence against ingested bacteria by reducing the acidity of the gastric contents. C. difficile spores are resistant to acid,
but vegetative cells are easily killed by gastric acid, reducing inocula by 99%. A study by Jump et al., (2007) found forms of \textit{C. difficile} survived exposure to gastric contents if the pH was greater than, or equal to, five. There is also risk of recurrent CDAD with the use of PPIs therapy. Patients receiving PPIs have been found to be 4.17 times more likely to have recurrence when compared to their counterparts not receiving PPIs (Cadle et al., 2007).

1.7.6 Pre existing illness

The suggestion that pre-existing mucosal injury pre-disposes to \textit{C. difficile} colonization is supported by the fact that patients with inflammatory bowel diseases (IBD) are at greater risk of acquiring CDAD than the general population (Issa et al., 2007). Two recent retrospective studies have reported a two-to threefold increase in the frequency of \textit{C. difficile} infection in patients with IBD over a five to six year period (Issa et al., 2007; Rodemann et al., 2007). These patient groups are exposed to many of the risk factors for CDAD. They are often prescribed antibiotics for treatment of other gastrointestinal pathogens and require frequent hospitalization for management of exacerbations of their IBD. In addition, many take immunosuppressive medications. CDAD in patients with IBD carries a higher risk of mortality than in patients without underlying IBD (Hookman & Barkin, 2009). A recent multivariate analysis reported that patients with IBD and \textit{C. difficile} had a fourfold higher mortality than patients admitted to hospital with IBD or \textit{C. difficile} alone. Higher mortality, more frequent endoscopy and surgery were found in patients with ulcerative colitis compared to Crohn’s disease (p < 0.05) who had associated \textit{C. difficile} (Ananthakrishnan et al., 2008).
1.7.7 Enteral tube feeding (ETF)

*C. difficile* can be a cause of diarrhoea during enteral tube feeding. One prospective cohort study of residents in a long term care facility demonstrated that ETF was an independent risk factor for *C. difficile* colonisation (Odds Ratio 6.5, p = 0.006) (Simor *et al.*, 1993). A prospective cohort study to determine the incidence of *C. difficile* acquisition and CDAD in tube fed and non-tube fed patients was conducted by Bliss *et al.*, (1998) Seventy-six patients receiving enteral tube feeding were matched for age, ward and disease severity with 76 patients not on enteral tube feeding. Acquisition of *C. difficile* was significantly greater in tube fed patients (p = 0.03) and more tube fed patients developed CDAD (p = 0.03). In this study, both patient groups were on high levels of antibiotics.

There are a number of proposed reasons for the association of CDAD with ETF. Firstly, enteral feeding provides a high frequency portal for inoculation of *C. difficile* spores deep into the gut (O'Keefe, 2010). Environmental factors have been proposed, as spores may be passed from the contaminated hands of healthcare workers during manipulation of the tube feeding system and following inadequate hygiene measures. There may also be contamination if decanting of formula is required, in the absence of adequate quality control protocols. The method of administration of enteral feeding may also play a role, with post-pyloric feeding increasing the risk, as feed is delivered below the gastric acid barrier and this may facilitate the introduction and survival of *C. difficile* organisms. Bliss *et al.*, (1998) reported that the incidence of CDAD was greater in tube fed patients who received post-pyloric tube feeding at some time during the study when compared to those who received pre-pyloric feeding continually or those without a feeding tube. It should also be noted that patients who
require enteral feeding, in particular those requiring post-pyloric feeding are usually sicker patients with a higher rate of complications and are more often on antibiotics.

1.7.8 Other risk factors
Cancer chemotherapy is another risk factor for the development of CDAD. The antimicrobial activity of several chemotherapeutic agents being thought to be the causative factor (Anand & Glatt, 1993). Increased risk is also thought to be linked to the immunosuppressive effects of neutropenia (Gorschluter et al., 2001). CDAD mortality rates are higher for Caucasian than other ethnic/racial groups. This has been attributed to the increased access to healthcare by elderly white people and to the fact that they are more likely to receive treatment with antibiotics and, as a result are at increased risk of developing C. difficile (Redelings et al., 2007).

1.8 Treatment for CDAD
There is no treatment required for asymptomatic carriers of CDAD (Johnson et al., 1992). For those who are symptomatic, the first approach in their treatment should be, if possible, discontinuation of the precipitating antibiotic(s). It has been shown that 15-23% of CDAD will resolve with the discontinuation of antibiotics (Teasley et al., 1983; Olson et al., 1994). Supportive therapy with replacement fluids and electrolytes may be required depending on disease severity. Antiperistaltic agents should be avoided as, theoretically, they can increase the risk of precipitating toxic megacolon by slowing the clearance of C. difficile toxin from the intestine (Aslam et al., 2005; Bouza et al., 2005). Metronidazole, vancomycin, teicoplanin and bacitracin have been used to treat CDAD. These antibiotics are known to inhibit C difficile growth and toxin production (Bricker et al., 2005). Most cases will respond to metronidazole or vancomycin and will show improvement of symptoms within one
to two days of starting therapy (Gerding, 2005). Treatment for ten days is indicated for mild CDAD (HPSC, 2008). Approximately 78-97% of patients treated for an initial infection will respond positively (Sunenshine & McDonald, 2006). However, in some cases, the *C. difficile* spores can remain in the gut even after aggressive treatment. Spores that remain hidden within the colonic diverticula can avoid gut peristalsis and antibiotic treatment (Tedesco *et al.*, 1985).

With the emergence of the B1/NAP1/027 strain and its associated increased virulence, interest in the disease has increased. Investigation into methods of preventing and treating the disease has intensified. A number of emerging therapeutic options for CDAD treatment are being developed. Medications used to treat other infections are being studied as alternatives to metronidazole and vancomycin. Due to the evidence that increased risk of recurrent CDAD is associated with poor host humoral response (Wilcox, 2004), the use of intravenous immunoglobulins to treat severe or refractory CDAD has had some promising results. For prevention of the spread of the bacterium, sporicidal cleaning agents have been developed. Probiotics are another of the options that are being studied for their role in both prevention and treatment of CDAD.
Part 2 – The prevalence of malnutrition in patients who develop *Clostridium difficile* associated disease

1.9 Malnutrition

Malnutrition is commonly defined as, ‘a state in which deficiency, excess or imbalance of energy, protein and other nutrients causes adverse effects on body form, function and clinical outcome’ (Stratton *et al.*, 2003). In recent years, there has been a greater understanding of the pathophysiology of malnutrition associated with disease or injury which is commonly observed in the clinical setting. The presence of inflammation results in an alteration of nutrient requirements, with the acute phase response resulting in an increase in energy expenditure and nitrogen excretion. Anorexia often accompanies inflammation and promotes further loss of lean tissue if nutritional intake is inadequate. In critical illness or injury, an acute inflammatory response occurs which has a rapid catabolic effect on lean body mass (Hill *et al.*, 1997). In the chronic disease state, the loss of muscle mass and function occurs at a slower rate over a longer period of time.

Representatives from the international clinical nutrition support community formed an International Guideline Consensus Committee and developed three aetio logically-based terms for the diagnosis of malnutrition in adults in the clinical setting. In chronic starvation without inflammation, the term ‘*starvation-related malnutrition*’ should be used. ‘*Chronic disease-related malnutrition*’ is the term recommended when chronic disease and mild to moderate inflammation are present. ‘*Acute disease or injury-related malnutrition*’ should be used when inflammation is acute and of a severe degree (Jensen *et al.*, 2010).
1.10 Malnutrition in the clinical setting

In health care facilities, there is evidence that malnutrition is present in 15-60% of patients (Stratton et al., 2003; Sorensen et al., 2008). Variation in prevalence data occurs because of different methods of nutritional assessment and different patient groups studied (Elia et al., 2005a). Irish data show that 11% of a mixed group of surgical and medical patients were malnourished (Corish et al., 2000). The most recent information on the prevalence of malnutrition in patients in Irish hospitals comes from the Nutrition Week Survey (NSW), conducted in January 2010. This data collection was part of a wider BAPEN survey which has an ongoing aim to obtain prevalence data on malnutrition. The Malnutrition Universal Screening Tool (MUST) was carried out on all new admissions complying with specified inclusion criteria 1,2 over a specific three day period. The nutritional status of 1602 patients was recorded in 29 hospitals and 17 care homes. One-third of patients were at risk of malnutrition (33%); 25% were at high risk and 8% at medium risk. These Irish results are very similar to those reported from the United Kingdom (UK) data (34% in UK hospitals found to be at risk of malnutrition) (Russell & Elia, 2011). Malnutrition was common in all types of hospitals, all types of wards, diagnostic groups and at all ages. Eighty-six percent of patients identified as at risk of malnutrition were admitted directly from home suggesting that the risk of malnutrition originates in the community (Russell et al., 2011).

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1 Inclusion criteria for Nutrition Screening Week (NSW) BAPEN: all adult patients admitted to medical, surgical, orthopaedic/trauma, care of the elderly, stroke and oncology wards between 00.01 hours on the 12th of January to 23.59 hours on the 14th of January 2010.
2 Exclusion criteria for NSW BAPEN: patient under 18 years of age, already established on nutrition support (oral nutritional supplements, Percutaneous Gastrostomy (PEG) feeding or Parenteral Nutrition)
1.11 The prevalence of malnutrition and CDAD
A number of the risk factors associated with the acquisition of *C. difficile* are also the risk factors associated with malnutrition. There is limited information in the literature on the prevalence of malnutrition in patients with CDAD. One study assessed prevalence of malnutrition using MUST in 76 patients at time of diagnosis of CDAD. In this group, 57% of the patients were malnourished (MUST score of 2 or more) (Wong *et al.*, 2008). No other studies have focused on the prevalence of malnutrition in this patient group and there are no Irish data available, although it is thought that prevalence is likely to be similar to that observed in the UK.

1.12 CDAD and risk factors for malnutrition

1.12.1 Increased age
As previously discussed, one of the risk factors for the acquisition of *C. difficile* is increased age. Although not observed in the recent Irish study (Russell & Elia, 2011), some studies have shown that elderly patients are more at risk of malnutrition than younger patients (McWhirter & Pennington, 1994). A number of reasons have been identified that contribute to the changes in body weight and composition of the elderly and which can result to the development of malnutrition. Physiological changes include age-related changes to the GIT. Selective neurodegeneration of the ageing enteric nervous system, resulting in symptoms of dysphagia, reflux and constipation, often occurs (Saffrey, 2004). Changes are also seen in the pancreas, liver and small intestine with increasing age (Popper, 1986; Dreiling *et al.*, 1991). There is a reduction in overall energy intake and this can occur due to a decrease in appetite and early satiety. Changes in satiety are a result of alterations to the GIT sensory function. There is also an impairment of the receptive relaxation of the gastric fundus, with rapid antral filling and distension (Morley, 2001). Daily food
intake has been reported to decrease by up to 30% between the ages of 20 to 80 years (Wurtman et al., 1988). The sense of smell is known to decline with age; this results in a reduced intake and interest in food. Hormonal alterations and the increased activity of cytokines are also linked to the anorexia that occurs with ageing.

Social factors such poverty, isolation and reduced ability to prepare and cook food can all have an impact on the nutritional status of older people living in the community setting (Ahmed & Haboubi, 2010). Dentition is often impaired with increasing age. There can be loss of teeth and, in cases where dentures are worn, ill-fitting dentures will impact on oral intake (Nakanishi et al., 1999).

Changes occur to body composition over time; body fat increases with a decrease in fat-free mass due to a loss of skeletal muscle (Prentice & Jebb, 2001). The increase in body fat with increasing age is related to reduced physical activity, reduced growth hormone secretion, diminished sex hormones and reduced resting metabolic rate observed in older people (Ahmed & Haboubi, 2010).

1.12.2 Length of hospital stay
A further risk factor to the development of malnutrition is length of hospital stay. Studies have shown that during a hospital admission, a patient’s nutritional status deteriorates and, as a result, those with a longer hospital stay are at increased risk of malnutrition. Several studies have found evidence to suggest that hospitalized patients receive less than optimal nutritional care due to lack of training and awareness of malnutrition among hospital staff (Dupertuis et al., 2003). During a hospital stay, patients are frequently placed nil per os (NPO) without being artificially fed, and this can occur on multiple occasions. Patients may undergo
procedures prior to, or during, meal service resulting in interruptions and/or missed meals, and meals can often be considered unpalatable.

Mc Whirter and Pennington (1994) investigated changes in nutritional status in general surgical and medical patients that occurred from hospital admission to discharge. Their study showed that 40% of patients were undernourished on admission. A further assessment on discharge indicated that a mean weight loss of 5.4% occurred as did a gradual decline in nutritional status in 14% of overweight, 26% of mildly malnourished and 37% of moderately malnourished patients. Braunschweig et al., (2000) observed a 31% decline in nutritional status from admission to discharge. Naber et al., (2004) investigated nutritional status on admission to, and discharge from, hospital using three methods of nutritional assessment including the Subjective Global Assessment (SGA). Using this classification, 45% of patients were classified as malnourished on admission and 51% were classified as malnourished on discharge. In a study carried out in patients admitted to two Dublin teaching hospitals, weight loss during the hospital stay occurred in 65% of the overweight and obese, 66% of normal weight and 43% of the underweight patients (Corish et al., 2000). It is difficult to compare these studies adequately due to the different methods of nutritional assessment used but overall, they indicate that the nutritional status of patients in hospital deteriorates during their period of hospital admission.

1.12.3 Enteral tube feeding (ETF)

As with older age and length of stay, the use of ETF is also associated with patients who are malnourished or at risk of malnutrition. ETF is used to feed patients who cannot attain adequate oral intake from food and/or oral nutritional supplements or
who cannot eat/drink safely. The National Institute of Clinical Excellence (NICE) guidelines (2006) state that healthcare professionals should consider ETF in people who are malnourished or at risk of malnutrition and have inadequate or unsafe oral intake and a functional, accessible gastrointestinal tract. Nutrition support should be considered in people who are malnourished as defined by any of the following:

- A Body Mass Index (BMI) less than 18.5 (kg/m$^2$);
- Unintentional weight loss greater than 10% in the last 3-6 months;
- BMI less than 20 (kg/m$^2$) and unintentional weight loss greater than 10% within the last 3-6 months.

NICE also provide guidelines for the introduction of nutrition support in people at risk of malnutrition, defined as follows:

- Have eaten little or nothing for more than 5 days and/or are likely to eat little or nothing for the next 5 days or longer;
- Have poor absorptive capacity and/or have high nutrient losses and/or have increased nutritional needs from causes such as catabolism.

In summary, ETF is used in those patients who are sicker and are at risk of malnutrition or who are malnourished.

1.13 Impact of malnutrition

Malnutrition is known to predispose to disease and adversely affect outcome. It has detrimental effects on both physical and psychological health (Stratton et al., 2003a). Malnutrition has been associated with higher rates of complications, and this has been shown in a number of studies as summarised in Table 1.1. These complications are associated with higher hospital costs (Messner et al., 1991; Correia & Waitzberg 2003) higher mortality (Coats et al., 1993; Correia & Waitzberg, 2003) and longer
hospital stay (Coats et al., 1993; Correia & Waitzberg, 2003). In the UK, the cost of malnutrition was calculated to be responsible for over 10% of the total health care budget. This is twice the amount that is spent on obesity and its related co-morbidities (Elia & Stratton, 2009). In Ireland, the cost of malnutrition on the health budget was calculated to be 10% of the €13.8 billion budget (Rice, 2010).

**Table 1.1 Physical and psychosocial effects of malnutrition**

<table>
<thead>
<tr>
<th>Adverse effect of malnutrition</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired immune response</td>
<td>Predisposes to infection</td>
</tr>
<tr>
<td>Reduced muscle strength and increased fatigue</td>
<td>Inactivity, inability to work effectively and poor self care</td>
</tr>
<tr>
<td>Reduced respiratory muscle strength</td>
<td>Poor cough pressure</td>
</tr>
<tr>
<td>Inactivity, especially in bed bound individuals</td>
<td>Predisposes to pressure ulcers and thrombo embolisms</td>
</tr>
<tr>
<td>Impaired thermoregulation</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Impaired wound healing</td>
<td>Increased wound infection, prolonged recovery from illness and increased length of hospital stay</td>
</tr>
<tr>
<td>Impaired psycho social function</td>
<td>Apathy, depression, self neglect</td>
</tr>
</tbody>
</table>

Source: Adapted from The “MUST” Report (Elia, 2003)

**1.14 Nutritional screening**

Nutritional screening is an assessment to identify those at risk of malnutrition and who require further nutritional assessment. All nutritional organisations and healthcare accrediting groups agree that nutrition screening is essential. It identifies those patients who are at nutritional risk so that appropriate nutritional assessment
and intervention can occur. Nutrition screening tools try to incorporate objective and subjective parameters that are sensitive to changes in nutritional status. It is accepted that no single marker is adequate and numerous factors have to be taken into account. There is no universal agreement on the best method of performing nutritional screening. Currently, many different measures are used, either alone or in combination, to gather information about an individual’s nutritional status. Green and Watson (2006) identified over 70 tests and tools to detect malnutrition. It is also believed that many unpublished screening tools are being used in the clinical setting. A number of the published screening tools have been critically reviewed and their advantages and disadvantages identified. Those commonly used are the SGA (Detsky et al., 1987), the Nutritional Risk Screening Tool (2002) – NRS 2002 (Kondrup et al., 2003a), the Mini Nutritional Assessment (MNA) (Guigoz et al., 1994) and MUST (Elia, 2003).

The European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines for nutritional screening recommend MUST, NRS-2002 and MNA (Kondrup et al., 2003b). Of the 29 Irish hospitals that participated in NSW (2010), 28% were using MUST and a further 6% were using MUST with the MNA or a local tool. Only 3% were using the MNA alone (Russell et al., 2011).

1.14.1 Malnutrition Universal Screening Tool (MUST)
MUST is the screening tool with the strongest support in the UK and Ireland. It is recommended as a screening tool by NICE, BAPEN and the British Dietetic Association (BDA). In 2008, the Irish Department of Health and Children strongly supported the use of MUST in Irish hospitals in the guideline document “Food and
nutritional care in hospitals, guidelines for preventing under-nutrition in acute hospitals” (Department of Health and Children, 2008).

MUST has been developed to detect protein-energy malnutrition and the risk of developing malnutrition using evidence based criteria (Elia, 2003). The three independent criteria used are; BMI, unintentional weight loss and acute disease effect producing or likely to produce no nutritional intake for greater than five days. Together, the three components are better predictors of outcome than the individual component (Elia, 2003). MUST has content validity (comprehensiveness of the tool), face validity (issues that are relevant to the purpose of the test) and internal consistency (Wood et al., 2004; Stratton et al. 2006). It has been shown to have predictor validity in the hospital setting for length of hospital stay, mortality and discharge destination. In the community setting, it has predictive validity for general practitioner visits and hospital admission in free living individuals (Stratton et al., 2002, Elia, 2003). It has excellent reproducibility between users in different healthcare settings across the UK (Elia, 2003) and has been shown to have excellent agreement with a dietitian’s assessment of malnutrition (Elia, 2003). In comparison with a number of other screening tools, MUST has been found to have “fair to good” to “excellent” concurrent validity (Elia et al., 2005a).

1.14.2 Mini Nutritional Assessment (MNA)

The original MNA was developed to provide a simple and reliable way to screen the nutritional status of persons over 65 years and to add a nutritional component to a comprehensive geriatric assessment. MNA screening is likely to identify risk of developing undernutrition at an early stage since it includes questions about physical and mental health which frequently affect the nutritional status of elderly. It is a
combination of a screening and an assessment tool. The predictive validity of MNA has been evaluated by demonstrating its association with adverse health outcomes (Ek et al., 1996), social functioning, mortality and higher rates of visits to the GP (Anderson et al., 1984; Berner, 2003). The tool has been validated specifically for the elderly (Guigoz et al., 1996) and has been found to be sensitive and reliable (Gazzotti et al., 2000; Bleda et al., 2002; Holm & Soderhamn, 2003). However MNA has a low efficacy with regard to predicting future malnutrition or adverse health outcomes for older people when screened at baseline (Rasmussen et al., 2010).

In 2001, the short form MNA (MNA –SF) was developed based on the original MNA. It was developed as a standalone screening tool and identifies malnutrition using 6 questions. The MNA – SF has been found to have 98% sensitivity, 100% specificity and 99% diagnostic accuracy for predicting malnutrition (Kaiser et al., 2009).
Part 3 - Probiotics and *Clostridium difficile* associated disease

1.15 Functional Foods

Probiotics, prebiotics and synbiotics are classified as a group of foods called ‘Functional Food’ (FF).

“A food can be regarded as ‘functional’ if it satisfactorily demonstrates to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is either an improved state of health and wellbeing and/or reduction of risk of disease” (Diplock *et al.*, 1999).

FF must remain a food, and it must demonstrate its effects in amounts that can be normally consumed in the diet (Diplock *et al.*, 1999).

1.15.1 Probiotics

Probiotics are live microorganisms that when administered in adequate amounts confer a beneficial effect on their host, by improving microbial balance and exerting health benefits beyond inherent general nutrition (FAO/WHO, 2001). The concept of probiotics emerged from observations early in the 19th century by the Russian immunologist, Elie Metchnikoff. He postulated that lactic acid bacteria offered health benefits and promoted longevity. In recent years, knowledge of the role of probiotics in health has increased. There is a growing body of scientific literature and a rise in the number of commercially available probiotic products. Numerous health effects are now associated with probiotic use. While some of these are well supported by evidence, probiotics are often used to treat conditions for which data regarding their efficacy is lacking or conflicting (Williams, 2010).
1.15.2 Prebiotics

Prebiotics are “selectively fermented ingredients that allow specific changes in both the composition and/or activity in the GIT microflora that confers benefit upon a host’s wellbeing and health” (Gibson et al., 2004). Fermentation of the prebiotics by endogenous anaerobic microorganisms occurs in the colon. Short chain carboxylic acids and lactic acid are produced and, these in turn, provide metabolic substrates for the colonocytes.

Prebiotics can occur naturally in foods or be added to food products. The common prebiotics include inulin, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), soya-oligosaccharides, xylo-oligosacchardies, pyrodextrins, isomalto-oligosaccharides and lactulose. The majority of studies have used FOS, GOS and inulin which have a long history of safe use. The reported benefits of prebiotics are still in the early stage of investigation but their efficacy has been examined in conditions such as constipation, diarrhoea, osteoporosis, obesity and type II diabetes mellitus (Roberfroid, 2000).

1.15.3 Synbiotics

Synbiotics are a mixture of prebiotics and probiotics. They beneficially affect the host by improving the survival and implantation of the live microbial dietary supplements in the GIT (Gibson et al., 2004). It is thought such products can potentially offer the properties of both probiotics and prebiotics. Some researchers feel that synbiotics should be more than a mixture of the two ingredients; that a synergy must exist between the ingredients (Jardine, 2009). To date most of the research has been on probiotics and prebiotics individually and there is less information about synbiotics.
1.16 Mechanism of action of probiotics
The mechanisms of action of probiotics remain an area of research. Many of the effects have been studied and established in animal models or in vitro assays. In humans, the direct demonstration of the effects of probiotics on relevant biomarkers is still incomplete (Rijkers et al., 2010). There are a number of proposed mechanisms through which probiotics could have an effect. Many have been shown to inhibit the growth and development of pathogenic bacteria, alter the composition of the GIT microflora and modulate the innate immune system. The suggested mechanisms for their effects on human health are proposed to be:

- Competitive inhibition of other organisms through competition for fermentable substrates and adhesion sites within the gut;
- Lowering gut pH through production of organic acids;
- Production of bacteriocins;
- Stimulation of the immune system;
- Regulation of gut motility;
- Strengthening gut barrier function;
- Binding and metabolism of toxic substances;
- Release of gut protective metabolites.

(O’Connell, 2009)

1.17 Probiotic availability
A probiotic is defined by its genus (e.g. Lactobacillus), its species (e.g. rhamnosus) and strain designation (often a letter or a number e.g. GG). Frequently, product manufacturers will generate a consumer friendly name; these names may be trademarked (™) or be a registered trademark (®) and are not the scientific name.
The FAO/WHO has a number of criteria that must be met for an organism to be classified as a probiotic. The organism must be characterised to strain level using phenotypic and genotypic techniques. There must be proof that the probiotic strain is safe for human consumption and is not contaminated in the form in which it is delivered. There should be evidence of its functional efficacy from in-vivo studies using animals and humans (FAO/WHO, 2002).

Probiotics are available in a wide range of commercial forms; capsules of freeze dried or lyophilized cultures, heat dried culture supernatants and mixed into dairy and other foods. They are available as a combination of organisms of varying quality and viability. The majority of commercial cultures for the food industry contain either \textit{Lactobacillus} species or \textit{Bifidobacterium} species. Some \textit{Escherichia, coli} (\textit{E. Coli}) species, \textit{Bacillus} species and yeasts are also used. In the last few years, the range of food products containing probiotics has increased considerably. Products are available in supermarkets, in health foods stores and on the internet. Europe traditionally has a strong position in the probiotic food market. In 1997, probiotic yogurts and milk accounted for 65% of the European FF market, with a market value of $889 million (Young, 1998). Daily dose dairy probiotic drinks are the largest growing probiotic product type in the European market (Saxelin, 2008). In Europe, \textit{Lactobacillus rhamnosus} GG (\textit{L. rhamnosus} GG) appears to be the most widely used probiotic on the food market. \textit{L. rhamnosus} GG containing foods are available in at least 15 European countries under various brand names (Saarela, 2009).

1.18 Commonly used probiotics
The most common probiotic genii used in food and in clinical trials are the bacteria Bifidobacteria and Lactobacilli and the yeast \textit{Sacharomyces boulardii}. Yeast
probiotics differ from bacterial probiotics in physiological structure, size and their impact on antibiotics, with yeast not being affected by antibiotics (Czerucka et al., 2007).

1.18.1 Bifidobacteria
Bifidobacteria are gram positive polymorphic rods. They are non-spore forming, non-motile and catalase-negative bacteria (O’Connell, 2009). Bifidobacteria have been widely used in food products for the past twenty years. There are upwards of 30 species of bifidobacteria identified (Leahy et al., 2005). They have been isolated from many sources such as sewage, human and animal faeces, and the rumen of cattle, dental caries and honey bees (Felis & Dellaglio, 2007). Bifidobacteria account for 3-6% of microflora in the GIT and are considered as key commensal bacteria in human microbial interactions, playing a pivotal role in a healthy GIT (Benno et al., 1984; Satokari et al., 2003). The proportion represented by bifidobacteria species varies between individuals and depends on lifestyle factors such as diet, exercise and stage of life. The dosage of bifidobacteria in food or other products can depend on the method of administration. The scientific literature appears to support a minimum probiotic dosage of $10^9$ colony forming units (CFU) per day if a measurable benefit to the host is to be observed (O’Connell, 2009).

1.18.2 Lactobacilli
Lactobacilli are gram positive, non-spore forming, catalyse-negative, usually non-motile and typically nitrate-reducing, rod-shaped bacteria. They utilise glucose fermentatively and may be homofermentative, thereby producing lactic acid from glucose or they may also be heterofermentative i.e. they can produce lactic acid, carbon dioxide, ethanol and/or acetic acid (Saarela, 2009). Their production of
organic acids and resultant lowering of pH gives them an advantage over other microbes (Saarela, 2009). In 2008, the number of lactobacilli species identified was around 120 (Saarela, 2009). However, this number is continually changing as new species are identified or some species are merged to form subspecies or transferred into another genus. Some species and strains are broadly used as starters and adjunct cultures to drive food and feed fermentation and have been used for thousands of years for this purpose. The notable products are dairy products (cheese and yogurts), fermented vegetables (olives, pickles and sauerkraut), fermented meats (salami and sausages), sourdough breads and other cereal-based commodities.

*L. rhamnosus* GG has received the most clinical attention to date. *L. rhamnosus* GG was discovered in 1985 by natural selection of healthy human microflora using the ideal characteristics of a probiotic (Silva et al., 1987). *L. rhamnosus* GG has been shown to secrete a low molecular weight compound that inhibits a broad spectrum of gram positive and negative bacteria and anaerobic bacteria (Silva et al., 1987). It has been shown to inhibit the attachment of *E. coli*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa* to uroepithelial cells and intestinal epithelial cells (Chan et al., 1985; Mack et al., 1999). It has also been found to suppress bacterial enzyme activity (Gorbach, 2000).

**1.18.3 Saccharomyces boulardii (S. boulardii)**

*S. boulardii* is the most common yeast used as a probiotic. Since its discovery in the 1920s by a French microbiologist, Henri Boulard, it has been used as a probiotic in Europe and has been investigated in clinical trials worldwide. *S. boulardii* is not endogenously found in the GIT of humans (Imhoff & Karpa, 2009). It has an optimum growth temperature of 37°C, is resistant to low pH and is tolerant to bile
acids (Fietto et al., 2004; Graff et al., 2008a; Pardo et al., 2009). Survival at this temperature makes it one of the few types of yeast able to live at human body temperature. *S. boulardii* is resistant to antibacterial agents and survives gastric acidity (Graff et al., 2008a; Buts, 2009).

*S. boulardii* is administered in capsules of lyophilized or heat dried product. When *S. boulardii* is given orally, it achieves a steady state concentration within three days and is cleared within three to five days following discontinuation (Blehaut et al., 1989; Elmer et al., 1999; Graff et al., 2008b). Lyophilized *S. boulardii* is distinct from dietary probiotic products and could be considered an example of a “probiotic drug” (Czerucka et al., 2007).

Studies in animals and cell models indicate *S. boulardii* has beneficial effects against a number of pathogenic toxins, preserves cellular physiology, interferes with pathogen attachment or assists in re-establishing short chain fatty acid (SCFA) levels. It may also act as an immune regulator both within the GIT lumen and systemically (McFarland, 2010). Castagliuolo et al., (1999) reported that 54 kDa serine protease produced by *S. boulardii* directly degrades *C. difficile* toxins A and B. It also produces proteases capable of degrading *C. difficile* toxin A and B receptor sites on the cell surfaces of enterocytes unlike any other strains of *Saccharomyces* (Pothoulakis et al., 1993; Castagliuolo et al., 1999). It has been proposed that once the toxin receptors have been acted upon by the protease, *C. difficile* is unable to produce disease as the bacterial toxins cannot attach to the inactivated receptor sites. This yeast may also stimulate chloride absorption and modulate *C. difficile* toxin B levels thereby reducing the symptoms of CDAD and permitting the re-establishment of normal GIT microflora. It is proposed that there has to be clearance of *C. difficile*
before there can be inactivation of toxin receptor sites by *S. boulardii* (McFarland *et al.*, 1994; Imhoff & Karpa, 2009). Two studies have shown *S. boulardii* has an effect on the immune system resulting in up-regulation of total and specific anti-toxin A secretory IgA expression in animal models of CDAD (Buts *et al.*, 1994; Qamar *et al.*, 2001). These actions of *S. boulardii* have lead to a number of trials investigating the role of the yeast in CDAD.

### 1.19 Dosage of probiotics

Commercially available products typically have at least $10^6$ CFU but may have as many as $10^{12}$ CFU (Verna & Lucak, 2010). Probiotics have a limited lifespan and, as a result, repeated dosing is needed to achieve constant concentrations within the GIT. One week after the discontinuation of oral probiotics, there are no longer detectable amounts in the stool (Spiller *et al.*, 2008).

Confusion occurs among the general public and health professionals as to which probiotics are best for good health. The wide range of probiotic strains in commercially available products and the quality control of probiotics are some of the reasons why confusion arises. Also, there is no consensus on the effective dosage of probiotics. In clinical trials, doses have varied from $10^7$ to $10^{11}$ per day. In most studies using the bacteria lactobacilli, the dose typically used ranged from 1-20 billion colony forming units per day (Williams, 2010). In the clinical trials with the yeast *S. boulardii*, the dose ranged from 250 to 300 mg per day for durations of between three days and six months (McFarland, 2010). In addition, different probiotic species and genii may have different immunological and physiological effects in various disease states (Verna & Lucak, 2010). In products providing a
combination of probiotics, the probiotics may interact and have a different impact on host intestinal microflora than if given as a single probiotic preparation.

As probiotics contain live organisms, the administration of antibiotics together with probiotics could kill a large number of the organisms and, as a result, reduce the efficacy of the probiotics (Williams, 2010). It has been recommended that patients consume bacteria derived probiotics separately from antibiotics, leaving at least a two hour gap between consumption. Anti-fungal medications may also interact with yeast probiotic products and reduce their efficacy (Williams, 2010). It is recommended by one commercial manufacturer that *S. boulardii* should not be taken with any oral systemic anti-fungal medications (Williams, 2010).

### 1.20 Regulation of probiotics

The regulation of probiotics depends on how they are to be consumed, for example whether they are included in a food, used as a dietary supplement or sold as an over-the-counter or prescribed medication. Within Europe, there are no defined lists of compounds that are accepted for use as prebiotics or probiotics. Quality assurance can also vary with the type of product, indication for use and country in which the product is sold. If the product makes a claim promising a health or nutritional benefit, this is regulated by European legislation. The legislation 2000/13/EC prohibits a company from stating that a foodstuff has the properties to prevent, treat or cure human disease or from making reference to any such properties. The regulation 2006/1924/EC on Nutrition and Health claims allowed on food products permits only standardised nutritional claims or specifically authorised health claims to be made. This regulation provides consumer assurance that misleading claims cannot be made. When a health claim is made, the format of the nutritional label is
specified in accordance with article 4(1) of Directive 90/496/EC. In Ireland, the Food Safety Authority of Ireland (FSAI) is responsible for the enforcement of all aspects of food legislation, including food labelling.

1.21 The variation of probiotics products
For optimal probiotic functionality, the probiotic product should contain sufficient quantities of the specific probiotic strain throughout the storage period until consumed. The pH, storage temperature and exposure to other microbes all impact on the viability and stability of the probiotic strain in a food product. How the products are manufactured may significantly affect the potency of the probiotic over time. Lyophilized products are stable at room temperature for one year provided they are protected from moisture (Graff et al., 2008a). Products containing heat dried probiotics must be refrigerated. All probiotic products should be stored according to manufacturers’ guidelines and all have a limited shelf life. Probiotic supplements produced by different manufacturers differ widely. Even the same product produced by the same manufacturer may vary due to the combination of probiotics they contain and bioactivity at the time of production.

Concerns have been expressed regarding the accuracy, quality and quantity of probiotic products available on the market. A number of studies have been conducted that illustrate the difficulties with product stability and labelling despite the legislation that exists to protect consumers. A gradual reduction in viable cell count occurs in probiotic products regardless of the producer’s expiry date, calling into question the accuracy of expiry dates on probiotic containers (Jayamanne & Adams, 2006). A study examined 58 probiotic products from Europe, the UK, Canada, Asia and Japan. Only 38% contained the dose described on the label and
29% did not contain strains listed on the label (Masco et al., 2005). A further study using polymerase chain reaction reported that two of five products tested contained no bifidobacteria and two of the products contained Lactobacilli that were not included on the product label (Drisko et al., 2005). A review of brewer’s yeast found the tablets contained no viable yeast at all (Sargent & Wickens, 2004). Marcobel et al., (2008) tested 14 commercial probiotic products and many of the probiotic products contained unadvertised additional lactobacilli and bifidobacteria, whereas, others were missing species listed on the product label. These findings would indicate that the manufacturers of probiotic products should be more tightly regulated and consumers must be wary of the product information on the products they are consuming.

1.22 Safety of probiotics

The safety of probiotics generally relates to the fact that they contain living organisms. Potential risks include transfer of antibiotic resistant genes, translocation of living organisms from the intestine to other areas of the body, persistence of the probiotic in the small or large bowel or the development of adverse reactions relating to interactions with the host microflora. The incidence of bacteraemia attributable to probiotic strains remains extremely low (Salminen et al., 2002), the estimated risk of developing bacteraemia from ingested Lactobacilli being less than 1 per million individuals (Borriello et al., 2003). The typical adverse reactions reported in clinical trials are mild to moderate nausea, vomiting, abdominal pain, cramps, rash, diarrhoea and constipation (Kligler & Cohrssen, 2008). Constipation and increased thirst have also been related to *S. boulardii* (Karpa, 2007) while the risk of developing fungaemia from *S. boulardii* is estimated at 1 per 5.6 million users (Karpa, 2007). A population based study in Finland found no increase in the number of cases of
*Lactobacillus* bacteraemia despite a massive increase in consumption of a product containing *L. rhamnosus* GG. The incidence of *Lactobacillus* bacteraemia was 0.3/100,000 inhabitants per year over a 5 year period (Salminen *et al.*, 2002; Salminen *et al.*, 2004). Williams (2010) commented that the overall risk of developing an infection from ingested probiotics is low, particularly in a generally healthy population.

Boyle *et al.*, (2006) suggest probiotics should be used cautiously in immune compromised individuals including those in a debilitated state or with malignancies. Caution should also be exercised in those with artificial heart valves, in patients with a history of rheumatic heart disease and those with central venous catheters. Any administration of probiotics to patients who are severely ill, in the intensive care setting or who have central line catheters should be monitored closely for episodes of unexplained fever (Buts, 2009). Concern has been expressed about the use of probiotics in pre-term infants (Boyle *et al.*, 2006). An increase in infectious complications could also be anticipated should probiotics be administered by jejunostomy, as this mode of delivery allows for an increase in the number of viable bacteria in the small intestine, as by passing of the acidic contents of the stomach occurs. *Lactobacillus* has been reported to cause bacteraemia in patients with short bowel syndrome, possibly due to altered gut integrity (Kligler & Cohrssen, 2008). *Lactobacillus* preparations are contra-indicated in patients with hypersensitivity to lactose or milk (Kligler & Cohrssen, 2008) while *S. boulardii* is contraindicated in patients with yeast allergy (Williams, 2010). Neither should it be taken with any systemic oral antifungal products. If patients are on antifungal medications, a
staggered dosing regimen is suggested if a decision is made to use probiotics (Elmer et al., 1995).

1.23 Consumer attitudes towards probiotics

Probiotics can be a very attractive option for patients for whom traditional pharmacological therapies can be marginally effective and their disease/illness is impacting on their quality of life. The current marketing of probiotic containing foods, together with the widespread availability of probiotics, reinforces the perception that probiotics are a ‘natural’ product. Individuals can commence this alternative therapy without any advice from a medical professional. However, studies would indicate consumer knowledge about these products is variable.

A focus group of 100 consumers was used to assess attitudes towards the probiotic cultures *Lactobacillus* and *Bifidobacterium* (Bruhn et al., 2002). Responses varied from those who were knowledgeable to those who were “repulsed” and unaware. Some individuals associated “culture” and “bacteria” with harmful bacteria and, therefore, expressed concern with their use. A number of consumers believed that probiotic cultures were unnecessary and a well balanced diet should provide the necessary bacteria. More detailed information on labelling and directions for consumption and the possible side effects from over consumption of probiotics was also raised as concerns by the group. In a Brazilian study, 34% of consumers defined probiotics as foods that contributed to weight reduction only, 29% defined them as foods that contributed to the intestinal environment while 21.5% of participants were unaware of the benefits of probiotics. Overall, the authors considered that consumers were confused about probiotic foods and their benefits (Vianna et al., 2008). A study of a New Zealand population found 25.4% of a random sample of consumers had
previously used probiotic products. The majority of the users had been recommended probiotics by the media but other common sources who recommended the products were friends and doctors (Schultz et al., 2011). A number of studies have found that probiotic users have similar profiles. There are more likely to be female (Block et al., 2007), educated (Block et al., 2007; Landstrom et al., 2007a), users of other non prescription supplements (Landstrom et al., 2007a) and also of European origin (Schultz & Lindstrom, 2008). From the perspective of the Irish population, a survey of Irish consumers was conducted in 2000 by Bogue and Ryan. 90% of respondents were aware of FF or the concept of FF. There was a high awareness of the benefits of FF ingredients such as calcium, vitamin C and iron but consumers were less familiar with the benefits of phytoestrogens, oligosaccharides and probiotics. Respondents would be more likely to purchase FF if there was more detailed information about the FF concept on the product label. As with previous studies of consumers, the authors concluded that the consumers did not fully understand the concept of FF and the associated benefits. Further qualitative research may help understand more about consumers’ perceptions of health enhancing foods and the various health messages generated by public health bodies (Bogue & Ryan, 2000).

1.24 Dietitians’ attitudes to probiotics
Dietitians are health professionals that assess, diagnose and treat, diet and nutrition related problems at an individual and wider public health level. Dietitians use the most up to date public health and scientific research on food, health and disease, which they then translate into practical guidance to enable people make appropriate lifestyle and food choices (BDA, 2010). Dietitians are the healthcare professional most likely to educate consumers and assist in scientific research into the benefits and effects of FF use (de Jong et al., 2004). They are in a key position to influence
consumers to use or avoid FF. There is no study examining dietitians’ beliefs or attitudes towards probiotics alone. There are a number of studies investigating their attitude towards FF, the group of foods into which probiotics are classified. The results from these studies have been mixed. An American study reported that in a group of 162 dietitians there was a positive view of FF. More than 80% of dietitians were confident about the effectiveness of FF in the prevention of illness and treatment of chronic illness, and at least 89% were confident of their safety (Lee et al., 2000). In a study of dietitians’, nurses’ and physicians’ trust in FF and their willingness to recommend them, dietitians were more willing to recommend FF than the other groups of health professionals studied. There was also greater trust and interest in the FF products among the dietitians when compared to the other two groups (Landstrom et al., 2007b). The need for scientific evidence for particular FF before recommending them to clients was required by the dietitians in this study however (Landstrom et al., 2007b).

In a Dutch study of dietitians, FF were considered useful only in specific cases with defined health problems. However, the authors concluded that confusion existed among dietitians about claims, safety, efficacy and the product handling aspects of FF (de Jong et al., 2004). McConnon et al., (2004) studied the differences in perception of FF between the public and nutritionists. There were some evident differences with the consumer being more worried about the benefits and the nutritionists being concerned over the control and responsibility of the products. An Irish study found consumers and dietitians had a similar perception of FF, but knowledge about FF was greater in the dietitians (Morrissey, 2007).
1.25 Dietitians’ knowledge of probiotics and professional practice

In Dutch dietitians 57% had a limited knowledge of FF (de Jong et al., 2004). Two thirds of a group of American dietitians were confident of the role of FF in the maintenance of good health and prevention of chronic diseases, but fewer dietitians were knowledgeable about the role in acute disease (Lee et al., 2000). The Dutch dietitians got most of their information from journals, magazine articles or the internet. Swedish dietitians got their information from scientific statements and the food industry (Landstrom et al., 2007b). There were varying findings among the groups on the practice among dietitians. Swedish dietitians were willing to recommend FF to patients (Landstrom et al., 2007b). American dietitians recommend FF for prevention rather than treatment (Lee et al., 2000). Nutritionists in the UK were hesitant to recommend FF possibly due to the lack of scientific evidence supporting some products (McConnon et al., 2004).

1.26 CDAD and probiotics

From a review of the mechanistic actions of probiotics, it can be seen that there are a number of ways that both bacterial and yeast probiotics could be of benefit in the prevention and treatment of CDAD. A large number of clinical trials and case studies have used different probiotic species, at varying doses and for differing lengths of time to assess their impact on the disease.

1.26.1 Probiotics in primary prevention of CDAD

The proposal that probiotics could replace the missing elements of the normal GIT in the prevention of CDAD has been investigated for nearly twenty years. There is relatively little evidence for a preventative role because of a lack of published data. The necessity to have large exclusion criteria, difficulty in recruiting adequate patient numbers to provide definitive evidence are the main issues in prevention studies.
Of the studies that have been published, many have had too few participants to show statistical significance between groups while many others have been poorly designed.

One study investigated the ability of $2 \times 10^{10}$ CFU per day of *Lactobacillus acidophilus* and *bifidobacterium* to prevent CDAD. Of the 138 patients recruited, 2.95% of the probiotic group were *C. difficile* positive compared to 7.25% of the placebo group. Even though the results look favorable, the study was inadequately powered to show statistically significant differences between the two groups. Another flaw identified in the study was that it may not have captured a true at risk patient group as patients requiring more than 20 days of antibiotic therapy were withdrawn from the study after day 20. It has been established that longer duration of antibiotic use is associated with greater risk of CDAD; therefore, in this study patients who developed CDAD past the 20 day period in both the treatment and control group were missed (Plummer *et al.*, 2004). Another observational analysis did suggest a benefit from a combination of lactobacilli/bifidobacteria in CDAD prevention. There was an estimated reduction in CDAD of 66%. There were limitations to the study results, as the data were gathered retrospectively and no placebo group was included in the study design. The fact that historical controls were used for comparison and that antibiotic usage and *C. difficile* strains may have changed over time, meant the groups could not be regarded as truly comparable (Graul *et al.*, 2009).

### 1.26.2 Probiotics in the prevention of antibiotic-associated diarrhoea (AAD) as a primary outcome, with CDAD as a secondary outcome

Several studies have investigated the capability of probiotics and yeasts to prevent antibiotic-associated diarrhoea (AAD) and, as a secondary outcome, have assessed
their effectiveness in the prevention of CDAD. The studies by Arvola et al., (1999), Thomas et al., (2001) and Plummer et al., (2004) had insufficient numbers to truly identify the benefits of probiotics in preventing CDAD. The yeast *S. boulardii* has been studied in four clinical trials for the prevention of AAD with positive outcomes (Surawicz et al., 1989a; Mc Farland et al., 1994; Kotowska et al., 2005; Can et al., 2006). The dose of *S. boulardii* used in these studies ranged from 500 mg to 1 g daily during antibiotic therapy or continued for up to two weeks after antibiotic therapy. When these studies were analysed to assess the role of *S. boulardii* in the prevention of CDAD as a secondary outcome, statistical significance was not achieved. In three of the studies, a trend towards significance was reported (Surawicz et al., 1989a; McFarland et al., 1994; Kotowska et al., 2005).

One randomized double-blind placebo-controlled trial did demonstrate a positive outcome from probiotics administered in the yogurt drink, Actimel™. Actimel™, contains a unique *Lactobacillus casei* strain, *Lactobacillus casei imunitass*, and two yoghurt associated bacteria *Streptococcus thermophilus* and *Lactobacillus bulgarius*. The drink was taken twice daily during antibiotic therapy and continued for one week after antibiotic therapy was discontinued. The subjects were over 50 years of age and were receiving either oral or intravenous antibiotics. A significant reduction in the incidence of AAD was observed in the probiotic group (p=0.007) and there was a significant reduction in the incidence of CDAD (p=0.001). No patient in the probiotic group and nine patients in the control group developed CDAD. The absolute risk reduction ratio was 17% (Hickson et al., 2007). Since publication of this study, it has been criticised. Wilcox & Sandoe (2007) state, that many patients were excluded if they were “too high risk” and had more than two recent courses of
antibiotics. Overall, only 7% of the patients screened were deemed eligible to participate in the trial. The control group received milk products which may have led to more episodes of diarrhoea as the lactose contained in the product could have triggered secondary lactose intolerance. Healthcare staff were not sufficiently blinded to treatment allocation as products were in different containers. It is also not clear that both groups were equally tested for *C. difficile* toxins when diarrhoea occurred. Another issue that has been raised is that *Streptococcus thermophilus* and *Lactobacillus bulgarius* are essential to the yogurt making processes and their sensitivity to bile makes survival and colonic colonization unlikely. Despite the initial promising results portrayed by this study, it does not appear to have the strength it was first thought to have.

### 1.26.3 Probiotics in prevention of recurrence of CDAD
There are some case reports and clinical trials investigating *Lactobacillus* and *S. boulardii* in the prevention of recurrent episodes of CDAD. Gorbach, in 1987, reported the use of *L. rhamnosus* GG (10^10 CFU) administered to five patients. These patients had suffered two to five relapses of CDAD over a two to five month period, despite antibiotic treatment. The treatment period with *L. rhamnosus* GG was seven to ten days. Of the patients treated, four had no further relapses and one patient improved initially but required a further dose of metronidazole. In another study, *L. rhamnosus* GG (5 x 10^9) at a dose of 125 mg was given twice daily for two weeks to four children, who had experienced three to five relapses of CDAD. All four children had a reduction in stool frequency. However, two children suffered relapses one to two months later requiring additional treatment (Biller *et al.*, 1995). Even though these are positive findings, limitations are inherent in these studies as
with all case reports and, caution should be exercised before drawing definitive conclusions.

Following the positive results from the case reports, two double-blinded, randomized, placebo-controlled trials were conducted using the *Lactobacillus* species. Wullt et al., (2003b) investigated the use of *Lactobacillus plantarum* 299v (5 x 10^{10} CFU/day) in patients who had one previous episode of CDAD in the previous two months. Patients were randomized to receive 400 mg of metronidazole orally three times daily for ten days and a fruit drink containing either the probiotic or placebo. Eleven of the twelve from the treatment group and all those in the placebo group achieved a clinical cure by days eleven to thirteen. In the follow up period, four of eleven patients (36.4%) who received the probiotics and six of nine patients (66.7%) in the placebo group experienced recurrence of CDAD symptoms; however, this result was not significant due to the study being inadequately powered. A further study by Lawrence *et al.*, (2005) investigated the role of *L. rhamnosus GG* in the prevention of recurrence of CDAD. Adults with recurrent CDAD were randomized to receive either 320 mg of inulin and *L. rhamnosus GG* (2.8 x 10^{11} CFU) or a placebo or 360 mg of inulin orally twice daily while on antibiotic therapy. The supplement was continued for an additional 21 days after the antibiotic therapy was concluded. In three of the eight *lactobacillus* patients, and one of the seven control patients, recurrence occurred. The *C. difficile* therapy also differed between the groups and additional systemic antibiotics and gastric suppressive therapies were used in individual subjects. The prebiotic, inulin, was used in both groups and may have prevented differences being observed between the groups (Imhoff & Karpa, 2009). Although these two studies were randomized and placebo-controlled, they
did not show positive outcomes for probiotics, perhaps due to the number of limitations previously described.

*S. boulardii* has been shown to have a more influential role in managing CDAD recurrence and there are some case reports and two positive double blind randomised control trials (RCT) using this yeast. In an open trial, there was successful eradication of CDAD in eleven of thirteen patients when *S. boulardii* was administered in combination with vancomycin (Surawicz et al., 1989a). Kimmey et al., (1990) reported on the case of 6 patients with recurrent CDAD; *S. boulardii* was commenced in the patients prior to discontinuing vancomycin therapy and continued for a further 3 months. There were no recurrences of diarrhoea or colitis while taking *S. boulardii* and this continued for a following 18 months. Following from this, two randomized double blind control trials were conducted. Mc Farland et al., (1994) recruited 60 patients with recurrent CDAD. *S. boulardii* was found to provide significant benefits, with nine of twenty-six patients (34.6%) experiencing recurrence in the probiotic group compared to twenty-two of thirty-four (64.7%) in the placebo group (p=0.04), a reduction in occurrence of 46.5%. There was a similar positive result in the trial conducted by Surawicz et al., (2002) during an eight week study. However, only when high dose vancomycin (high dose = 2 g vancomycin, low dose = 500 mg vancomycin) was administered in conjunction with *S. boulardii*, did the yeast significantly reduce the recurrence of CDAD. Three of the eighteen *S. boulardii* patients (16.7%) experienced recurrence compared to seven of fourteen (50%) of the patients receiving high dose vancomycin and placebo (p=0.05). In a 5-month follow up period, of those who received the probiotic and high dose vancomycin, none of the 16 followed up experienced recurrence, while 3/13 (23%)
of those given the placebo and high dose vancomycin experienced recurrence. These two studies do show positive results and promise for the role of *S. boulardii* in the prevention of CDAD recurrence. However, in the literature a number of valid flaws have been identified in these two studies and are discussed in a review paper by Miller (2009). In the study by Mc Farland *et al.*, (1994) the study design did not control for the dose or the duration of antibiotic. There was no benefit of the probiotic in patients who had developed CDAD for the first time. The benefit occurred only in the patients with recurrent CDAD. Furthermore, this study was conducted before the NAP1/027/BI strain had been identified, so its potential benefit on the current outbreaks of CDAD may not be as large. In the second study conducted by Surawicz *et al.*, (2000) the antibiotic therapy was not randomized in the probiotic and placebo groups. The benefits were only seen in a sub-group of patients in a study that already had a small number of patients. Safety concerns about the use of *S. boulardii* in certain groups of patients are often quoted as reasons why the routine use of this yeast in the prevention of CDAD recurrence is not yet fully supported (Bauer *et al.*, 2009).

1.26.4 Meta-analyses of probiotics and CDAD

The studies discussed previously have been included in a number of meta-analyses examining the efficacy of probiotics in CDAD. Dendukuri *et al.*, (2005) conducted a systematic review, four studies were included. The benefit of probiotic therapy seen in two studies was restricted to subgroups characterized by severe CDAD and higher doses of vancomycin (McFarland *et al.*, 1994; Plummer *et al.*, 2004). The authors considered that the two other studies were methodologically flawed (Surawicz *et al.*, 2000; Wullt *et al.*, 2003b). Of the studies conducted in which the prevention of CDAD was a secondary outcome, four studies were identified (Surawicz *et al.*, 2000; Wullt *et al.*, 2003b).
1989a; McFarland et al., 1995; Lewis et al., 1998; Thomas et al., 2001). These studies had too few cases of CDAD and provided no evidence for probiotic prophylaxis. The conclusion from the review was that there was insufficient evidence to support the use of probiotics in the prevention and treatment of CDAD and further better designed and larger studies were required.

A meta analysis was conducted by Mc Farland (2006), again looking at the role of probiotics for the prevention of AAD and the treatment of CDAD. The review reported on the analysis of six RCT’s, the probiotics had a significant efficacy in the treatment of CDAD (RR=0.59, 95% CI 0.41, 0.85 p=0.005). Only S. boulardii was effective for treating CDAD. The author concluded that a number of different probiotics strains showed promise as effective therapy for AAD and CDAD. However, this analysis was criticized in letters to the editor by (Lewis, 2007) and Dendurkuri (2007) who stated that both prevention and treatment studies were combined, and the “pooled” odds ratio was driven by a single positive study. Dendurkuri (2007) further commented that uncritical reading of Mc Farland’s meta-analysis was “misleading and risked the use of possibly ineffective, potentially hazardous therapies”.

In 2008, a Cochrane review was conducted on the role of probiotics for the treatment of C. difficile associated colitis. Only four studies met the inclusion criteria and the data could not be pooled because of variations in patient recruitment, the types of probiotics used, high dropout rates and variations in concomitant antibiotic therapy. From the data analysed, the two conclusions reached were that firstly; “probiotics are an unproven alternative or addition to antibiotics to cure infection
with *C. difficile*” and “the studies used did not provide enough evidence to support the use of probiotics for treating *C. difficile* infection” (Pillai & Nelson, 2008).
1.27 Conclusion
CDAD is the most common cause of nosocomial infection, typically resulting in symptoms of diarrhoea, abdominal cramps and fever, all of which compromise the health of the vulnerable hospitalized patient. In recent years, with the emergence of new virulent strains, the disease has become more severe and resistant to treatment. Research into all aspects of the disease remains ongoing.

To have accurate information on the nutritional status of this patient group is important. Although the prevalence of malnutrition in many disease states has been well documented in the literature, yet there are little data available on the nutritional status of patients with CDAD. Nonetheless, it is logical to assume that malnutrition occurs frequently in this patient group, particularly when the risk factors of prolonged hospital stay; ETF and increasing age are associated with both the acquisition of CDAD and with the development of malnutrition. The aim of this research was, therefore, to investigate the nutritional status of Irish patients who develop CDAD and to compare these data with those of medical and surgical patients within the same hospital and to published Irish data on the prevalence of malnutrition.

The use of probiotics for the prevention and treatment of CDAD is relevant to the professional practice of dietitians. To date, the scientific evidence for their efficacy shows promise but conclusive evidence remains unavailable. Some studies surveyed dietitians’ opinions and use of FF, however none have specifically looked at their use of probiotics. With a large range of commercial products available and an emerging body of research in probiotics, it is important to establish that the practices of
dietitians are evidence-based, safe and consistent. This study will investigate Irish dietitians’ opinions and recommendations for the use of probiotics in patients with CDAD and other clinical conditions. Information about probiotic products being recommended and used within Irish healthcare facilities and the factors that influence probiotic selection will be obtained.
CHAPTER 2 - Prevalence of malnutrition in patients who develop CDAD
2.1 Introduction

*Clostridium difficile* is the most common cause of diarrhoea resulting from nosocomial infections (Johnson & Gerding, 1998). There are a number of identifiable risk factors for its acquisition; of these, advanced age and length of hospital stay also predispose to malnutrition. It has been well established that the presence of malnutrition is detrimental physiologically and clinically, impairing quality of life and delaying recovery from illness (Stratton *et al.*, 2003). Data suggest that disease-related malnutrition doubles the risk of mortality in hospital patients and triples mortality in older patients (over 65 years) both in hospital and following discharge (Stratton *et al.*, 2006a; Stratton *et al.*, 2006b). One UK study reported that 57% of patients (n = 76) were malnourished at time of diagnosis of CDAD (as per MUST classification) (Wong *et al.*, 2008). Although it is generally assumed that patients who develop CDAD are at increased risk of malnutrition, there is little information in the literature to substantiate this. There are no data available on the nutritional status of Irish patients who develop this condition and how this compares to other patients admitted to hospital.

Nutritional screening is an assessment to identify those at risk of malnutrition and who require further nutritional assessment. MUST has been developed to detect protein-energy malnutrition and the risk of developing malnutrition using evidence-based criteria (Elia, 2003). MUST takes into consideration three factors: BMI, weight change and food intake and assigns equal weight to these three components, as they have been shown to have statistically significant effects when considered individually or together. BMI indicates chronic protein-energy malnutrition; however, this alone will not always detect patients at risk of malnutrition. Change in weight reflects an acute change in protein energy status and unintentional weight loss.
from outside the normal intra-individual range suggests the presence of underlying disease processes or psychological problems that predispose to malnutrition. Recent weight loss in ill patients is correlated with undernutrition-related complications and these, in turn, are linked to poorer healthcare outcomes. Diminished food intake also predicts deterioration in nutritional status.

2.2 Aims
The aim of this study was to assess the prevalence of malnutrition using the MUST screening tool in patients at St Vincent’s University Hospital on diagnosis of *C. difficile* associated disease (CDAD group) and to compare this to the prevalence of malnutrition observed in a comparison group of patients in the same hospital.
2.3 Methods and Materials

2.3.1 Study Design and setting
This was a prospective study in which all data were collected in a major academic teaching hospital in Dublin, St Vincent’s University Hospital (SVUH). The hospital has 479 inpatient beds and admits both medical and surgical patients.

Initially, the data collection for this study was one component of a collaborative research project between the microbiology department of SVUH and the care of the elderly department of the Mater Misericordiae Hospital, Dublin. This research project was titled “Immune Response and Molecular Epidemiology of Clostridium difficile-associated Diarrhoea (CDAD): A Prospective Study.” The collaborative study set out to establish:

1. The epidemiology of prevalent C. difficile strains using molecular typing methods and, from this information, the outcomes of infection and the rates of re-infection versus relapse in recurrent CDAD;
2. The immune response to C. difficile surface layer proteins and their importance in predicting recurrent diarrhoea and/or disease severity;
3. The genetic determinants of the innate and acquired immune response to C. difficile.

Nutritional information (weight, height, BMI, Mini Nutritional Assessment (Appendix 1)) and method of nutritional intake) was one aspect of the data collected for the collaborative research project. These data were collected by the research dietitian (YH) for 16 cases on the SUVH site. Data gathered for completion of the
screening tool MUST (Appendix 2) were also collected. As the desired number of patients for the collaborative research study had been achieved by March 2009, further subject recruitment \((n = 18)\) in SVUH continued independent of the SVUH/Mater collaborative research project.

Data on the comparison group were gathered during a one day MUST compliance audit that was conducted by the SVUH multidisciplinary Nutrition Committee in November 2010. The data were collected by a multidisciplinary group that included the research dietitian.

### 2.3.2 Ethical approval

Ethical approval to carry out this study was granted by the ethics committee of the Dublin Institute of Technology [DIT reference 74/08] and the ethical and medical research committee for St Vincent’s Healthcare Group. The audit committee of St Vincent’s Healthcare Group and the SVUH Nutrition Committee granted permission to use the data collected in the MUST compliance audit for the purpose of providing a comparison group for this study.

### 2.3.3 Participants

Patients in the CDAD group were in-patients in SVUH who had a stool sample positive for \textit{C. difficile} toxin A or B. Initially, the subjects were identified by the researchers working on the collaborative SVUH/Mater project. Once the subject had given consent to participate, the dietitian was informed and the nutritional data were collected. For the remaining subjects, the dietitian identified patients by regular contact with the microbiology laboratory. Subjects were recruited between August 2008 and May 2010. Not all patients diagnosed with CDAD during this time were recruited. This was due to re-submission to the ethics committee in SVUH for
further permission for patient recruitment and also occasional difficulties in the system of identifying patients with CDAD.

The comparison group patients were a group of patients from five wards (two surgical and three medical) who were hospital inpatients on the audit date (total of 94 beds). The length of stay of these patients prior to audit varied. The data were collected on the 24th November, 2010. Only patients for whom the date of admission was available were included in the hospital comparison group (n = 59 patients were audited on the day). Due to time limitations matching for the age and sex of the comparison group to the CDAD was not possible. The other hospital patient group was hoped to reflect a general hospital patient, with varying age, clinical conditions and length of stay.

In the CDAD group 34 subjects were recruited and there were 36 subjects recruited for the hospital comparison group.

2.3.4 Exclusion criteria

2.3.4.1 CDAD group
Patients were excluded if they were under 18 years of age or outpatients. Patients were not included if they were already enrolled in another investigational study or clinical trial and if, at time of diagnosis, were patients in ICU.

2.3.4.2 Hospital comparison group
Patients who were deemed too unwell or were not at their bedside at the time of audit were excluded. Patient suitability was based on the discretion of those collecting the data in consultation with ward nursing staff.
2.3.5 Consent

2.3.5.1 CDAD group
In the CDAD patient group, a consent form was signed by both the participant and
the research dietitian and was filed in the patient’s medical notes (Appendix 3). In
cases where patients were unable to give written consent, the next of kin was
contacted and verbal consent was obtained and documented on the consent form and
filed in the medical notes.

2.3.5.2 Hospital comparison group
As agreed with the Audit and Nutrition Committees in SVUH, verbal consent for the
data collected for the MUST audit to be used as comparison group data for this study
was deemed sufficient. This was provided by all patients who participated in the
MUST audit.

2.3.6 Data collection
Detailed clinical data were obtained in the CDAD group within 72 hours of diagnosis
of CDAD. All data for the comparison group was collected on the 24th of November
2010. For each case in both groups, baseline demographic details of age, gender and
date of admission were collected. Information was determined by patient interview,
medical chart review and review of nursing records. The data collection, patient
interview and anthropometric measurements were conducted by the research dietitian
for the CDAD group. For the comparison group, the data were collected by a
member of the multidisciplinary audit team that included the research dietitian.
Patients were allocated into diagnostic categories in accordance with BAPEN NSW
recommendations for diagnostic categories. The diagnostic categories are systems
based, and in patients with infection or cancer they are included within the relevant
diagnostic category. The eight categories are central nervous system, gastrointestinal, respiratory, cardiovascular, genito/renal, musculoskeletal, others and not known. Information was recorded on a standardised form for both groups (CDAD group, Appendix 4; Hospital comparison group, Appendix 5). All patient identifiers were removed and each patient was allocated a unique study number.

### 2.3.6.1 Nutritional Assessment

The main outcome measure of this study was the assessment of nutritional risk in patients with CDAD. Although there is no universally accepted definition of malnutrition nor is any one screening tool accepted as a gold standard, the MUST screening tool was selected to determine nutritional risk in this study. This screening tool is supported by the UK and Irish Departments of Health and expert bodies in both countries (BAPEN, ISPEN, INDI, and Nutrition Society). Within the study hospital itself, MUST has been shown to perform well against the previously used screening tool and other commonly advocated tools (Keaskin et al., 2010). MUST takes into consideration three independent criteria and has been shown to have excellent agreement with a dietitian’s assessment of malnutrition. Additionally, advantages to its use include surrogate measures for current and previous weight and height. This is particularly useful in patients with CDAD, as this group is older and frequently frail or bedbound.

### 2.3.6.2 Anthropometry

The weighing of subjects was conducted where possible by the research dietitian or member of the audit team. Weight was measured to the nearest 0.01 kilogramme using ward scales (CDAD, n = 28; hospital comparison group, n = 32). Scales used in SVUH are Seca 710 electronic column scales and Seca 955 electronic chair scales.
All hospital scales are calibrated annually. In cases where patients could not be measured accurately, recalled weight (if reliable and realistic) was used (CDAD, n = 6; hospital comparison group, n = 4) (Elia 2003, Stratton et al., 2003).

To obtain height in patients who were mobile and able to stand, height was measured using a wall mounted stadiometer (Seca 220, Hamburg, Germany or Seca 222, Hamburg, Germany) according to standard methodology (Elia, 2003) (CDAD, n = 2; hospital comparison group, n = 9). The subject’s height was measured with the patient standing straight and stretched, heels against the wall and the measurement taken with the head in the Frankfort Plane position. In patients that were unable to stand, ulna length (CDAD, n = 23; hospital comparison group, n = 18) was used to calculate height. To calculate the patient’s ulna length, the patient’s arm (left) was bent diagonally across the chest, with the palm is facing inwards and fingers pointing towards the shoulders. The measurement is taken using a measuring tape (Seca 201, Hamburg, Germany) between the central and most prominent parts on the styloid process and the centre of the olecranon at the elbow. If ulna length was not able to be conducted, recalled height was asked and used if deemed to be reliable and realistic (CDAD, n = 9, hospital comparison group n = 9) (Elia, 2003; Stratton et al., 2003).

2.3.6.3 MUST classification
For both patient groups, MUST was completed in accordance with the guidance document (Elia, 2003). For step one, the weight and height obtained for the patient was used to determine the patient’s BMI (weight (kg)/ height (m²)) and was scored according to MUST classification. For step two of MUST, three methods were used
to obtain the percentage of unplanned weight loss in the previous 3-6 months. Where previous weights were documented in patients’ notes the difference from current to previous weight was calculated (CDAD, n = 15; hospital comparison group, n = 8). If a weight history was not documented, the patient was asked about their weight history for the previous 3-6 months (CDAD, n = 15; hospital comparison group, n = 22). In subjects where reliable records or reports could not be obtained, subjective criteria (the presence of loose fitting clothes or jewellery) was used (CDAD, n = 4; hospital comparison group, n = 6). To determine a score for step three of MUST (the acute disease affect on inability for nutritional intake for greater than 5 days) in both patient groups, a combination of patient interview, review of the medical and nursing notes and information from the nursing staff was used.

2.3.6. 4 MNA – CDAD group
For completion of the MNA screening tool the anthropometric details required for current BMI (questions b) and weight loss (question f) were gathered in accordance with the methods described above. Details required for the assessment questions on current oral intake (question a), mobility (question c), psychological problems (question d) and neuropsychological problems (question e) were obtained from patient interview, nursing and medical notes and nursing staff.

2.3.7 Hygiene
All hygiene guidelines for dealing with patients and equipment were adhered to as per HPSC C. difficile document (HPSC, 2008) (Appendix 6) and the SVUH infection control manual (Appendix 7).
2.3.8 Statistical analysis
Data from the standardised forms from both groups were entered and stored on a Microsoft Excel (version 2007) database (Microsoft Corporation, Redmond, Washington). For statistical analysis, a codebook was prepared. Each variable was given a unique variable name and a numerical code was assigned to all applicable variables (hospital comparison / CDAD group, gender and ward classification). The data set was transferred to the Statistical Package for Social Sciences (SPSS) for Windows Version 19 (IMB, SPSS Statistics, United States) for analysis. All data were checked prior to analysis being performed. For categorical variables (sex, CDAD/ hospital comparison group, ward and diagnostic criteria), frequencies were analysed, maximum and minimum values were reviewed and it was established if any cases were missing. For the continuous variables (age, length of stay (LOS), MUST, BMI, weight and height), descriptive statistics were reviewed for out of range values indicating incorrect figures or errors in the database. The characteristics of both the CDAD and hospital comparison patient groups were described using descriptive statistics. The normality of distribution of continuous variables in both datasets was assessed using the result of the Kolmogorov-Smirnov test in conjunction with an assessment of histograms, skewness and kurtosis values. As the distribution of all continuous variables was skewed, the Mann-Whitney U-test was used to test for differences in continuous variables (age, weight, LOS, MUST and BMI) between the CDAD and comparison groups. Chi-squared (or Fishers Exact Probability) tests were used to investigate differences between categorical variables (sex, ward and diagnostic criteria) in both groups. Direct logistic regression was performed to assess the impact of four variables (age, sex, BMI and MUST) on the
likelihood of having CDAD. Statistical significance was set at a probability of less than 5% (p < 0.05).
2.4 Results

2.4.1 Subjects characteristics
All details for age, gender and date of admission were collected on 34 patients in the CDAD group and 36 patients in the hospital comparison group. Of patients in the CDAD group, 14.7% (n = 5) were diagnosed with CDAD on admission to hospital, the remaining patients in this group acquired *C. difficile* during their hospital admission. Table 2.1 describes the patient characteristics. There was a statistical difference in the age of the patients in each group (p = 0.002) with 85% (n = 29) of patients in the CDAD group aged sixty five years or older compared to 50% (n = 18) in the hospital comparison group. There was no difference in LOS or primary diagnosis between the two groups. There was a trend towards significance between the groups in gender (p = 0.082) and if medical or surgical patients in the groups (p = 0.057).
Table 2.1 Subject characteristics of CDAD and hospital comparison group

<table>
<thead>
<tr>
<th></th>
<th>CDAD group</th>
<th>Hospital Comparison group</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 34</td>
<td>n = 36</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24 (70.6)</td>
<td>17 (47.2)</td>
<td>0.0821</td>
</tr>
<tr>
<td>Male</td>
<td>10 (29.4)</td>
<td>19 (52.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>82 (72 -86.3)</td>
<td>64.5 (53.5 -77)</td>
<td>0.0022</td>
</tr>
<tr>
<td><strong>Ward Location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>21(61.8)</td>
<td>13 (36.1)</td>
<td>0.0571</td>
</tr>
<tr>
<td>Surgical</td>
<td>13 (38.2)</td>
<td>23 (63.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Length of Stay (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>12.5 (3.8 -29.8)</td>
<td>15 (10 -28.5)</td>
<td>0.3472</td>
</tr>
<tr>
<td><strong>Primary Diagnosis:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>1 (2.9)</td>
<td>4 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>9 (26.5)</td>
<td>11 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>4 (11.8)</td>
<td>3 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>10 (29.4)</td>
<td>4 (11.1)</td>
<td>0.1111</td>
</tr>
<tr>
<td>Genitourinary/renal</td>
<td>3 (8.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>3 (8.8)</td>
<td>8 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (11.8)</td>
<td>6 (16.7)</td>
<td></td>
</tr>
</tbody>
</table>

kg (kilogramme)

*p < 0.05 = statistically significant

1Chi-squared test used to determine difference between groups; 2Mann-Whitney U test used to determine difference between groups
2.4.2 Risk of malnutrition
Malnutrition or risk of malnutrition was observed in 75.5% of the CDAD group and 66.7% of the hospital comparison group as classified by a MUST score of 1 or more. This classification includes those at medium and high risk of malnutrition. There was no statistical difference between the CDAD and hospital comparison group. Table 2.2 describes the nutritional status of patients in each group. In the CDAD group, underweight (BMI < 20 kg/m\(^2\)) contributed to 38% of patients being classified as “malnourished” (medium to high risk). In the hospital comparison group, only 22.2% were underweight using BMI < 20 kg/m\(^2\). Of patients in the CDAD group, 26.5% had a BMI less than 18.5 kg/m\(^2\) while in the comparison group, 13.9% had a BMI less than 18.5 kg/m\(^2\). Although the MNA identified a greater number of CDAD patients as malnourished or at risk of malnutrition (85.3% compared to 75.5% identified using MUST), this was not statistically significant (p = 0.207). Table 2.3 describes a subgroup of those aged 65 years in the CDAD and hospital comparison group. No significant difference between the weight, BMI and MUST scores in this sub group.
Table 2.2 Nutritional status of CDAD and hospital comparison group

<table>
<thead>
<tr>
<th></th>
<th>CDAD group</th>
<th>Hospital Comparison</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 34</td>
<td>n = 36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (inter quartile range)</td>
<td>57.2 (47.3-68.0)</td>
<td>70.1 (56.9-83.4)</td>
<td>0.0041</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (inter quartile range)</td>
<td>21.0 (18.2-25.1)</td>
<td>24.15 (20.5-29.6)</td>
<td>0.0151</td>
</tr>
<tr>
<td>&lt;20</td>
<td>14 (41.2)</td>
<td>8 (22.2)</td>
<td>0.8111</td>
</tr>
<tr>
<td>20-24.9</td>
<td>11 (32.4)</td>
<td>11 (30.6)</td>
<td>0.8291</td>
</tr>
<tr>
<td>&gt;25</td>
<td>9 (26.5)</td>
<td>17 (47.2)</td>
<td>0.1371</td>
</tr>
<tr>
<td><strong>MUST</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0 = low risk</td>
<td>8 (23.5)</td>
<td>12 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Score 1 = medium risk</td>
<td>6 (16.7)</td>
<td>6 (16.7)</td>
<td>0.2671</td>
</tr>
<tr>
<td>Score 2 = malnourished or high risk</td>
<td>20 (58.8)</td>
<td>18 (50)</td>
<td></td>
</tr>
<tr>
<td><strong>MNA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0-7 (malnourished)</td>
<td>18 (52.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 8-11 (at risk of malnutrition)</td>
<td>11 (32.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 12-14 (normal nutritional status)</td>
<td>5 (14.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05 = significant
1Mann-Whitney U test used to determine difference between groups
Table 2.3 Nutritional status of CDAD and hospital comparison group of subjects aged 65 years and older

|                      | CDAD group | Hospital Comparison group | p value*  \
|----------------------|------------|---------------------------|-----------
|                       | n = 29     | n = 18                    |           \
| n (%)                |            |                          |           \
| Weight (kg)          | Median (inter quartile range) | 57.0 (47.1-68.5) | 58.8 (54.0-74.1) | 0.260^1 \
| BMI (kg/m^2)         | Median (inter quartile range) | 21.2 (18.2-25.3) | 22.2 (19.1-28.9) | 0.364^1 \
| >20                  | 12 (41.4)  | 5 (27.8)                  | 0.916^1   \
| 20-24.9              | 10 (34.5)  | 8 (44.4)                  | 0.894^1   \
| >25                  | 7 (24.1)   | 5 (27.8)                  | 0.060^1   \
| MUST                 |            |                          |           \
| Score 0 = low risk   | 0 (0)      | 0 (0)                     |           \
| Score 1 = medium risk| 7 (24.1)  | 5 (27.8)                  | 0.681^1   \
| Score 2 = malnourished or high risk | 22 (75.9) | 13 (72.2) |           \

*p < 0.05 = significant
1Mann-Whitney U test used to determine difference between groups

2.4.3 Nutritional intake in CDAD group

Five patients were receiving ETF at the time of the study assessment. Two of these patients were NPO and the remaining three were consuming some oral diet supplemented with oral nutrition supplements (ONS). All five patients were receiving a polymeric enteral feed and only one patient was not being provided with a source of fibre from the feed. Of those patients in the CDAD group, 47% were
prescribed ONS in addition to their hospital diet. In each case, the ONS prescribed were polymeric.

Two patients were prescribed a multivitamin and mineral supplement, and nine patients were prescribed probiotics, the dose ranging from once per day to three times per day. Either “probiotics” (n = 3) or “Everybody” (n = 6) was written in the medication kardex. There was no reference made to the probiotic strain.

2.4.4 Dietetic referral of CDAD patients
At the time of the study assessment, 55.5% (20 patients) with CDAD had been referred to a dietitian. Of those referred, 65% (13 patients) had been prescribed ONS. All five tube-fed patients had been referred; two were on nasogastric (NG) feeds and three were on NG feeds to supplement their oral intake and had also been prescribed ONS. 30% (6 of the 20 patients) in the CDAD group that were classified as high risk of malnutrition (i.e. with a MUST score of 2) had not been referred a dietitian.

2.4.5 Direct logistic regression
Direct logistic regression was performed to assess the impact of a number of factors on the likelihood of having CDAD. The model contained four variables (sex, age, BMI and MUST), the full model containing all predictors was statistically significant $\chi^2 (4 \ n = 70) = 15.11, \ p =0.04$ indicating that the model was able to distinguish between respondents who had CDAD and were the comparison group. The model as a whole explained between 19.4% (Cox and Snell R square) and 25.9% (Nagelkerke R squared) of the variance in CDAD status, and correctly classified 51.4% of cases.

As shown in table 2.4 only age made a unique statistical significant contribution to the model ($p = 0.043$).
Table 2.4 Direct logistic regression predicting likelihood of reporting CDAD

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>Df</th>
<th>p</th>
<th>Odds ratio</th>
<th>95.0 % C.I for Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>0.036</td>
<td>0.018</td>
<td>4.092</td>
<td>1</td>
<td>0.043</td>
<td>1.037</td>
<td>1.001</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>-0.095</td>
<td>0.063</td>
<td>2.285</td>
<td>1</td>
<td>0.131</td>
<td>0.909</td>
<td>0.803</td>
</tr>
<tr>
<td><strong>MUST</strong></td>
<td>0.062</td>
<td>0.205</td>
<td>0.092</td>
<td>1</td>
<td>0.762</td>
<td>1.064</td>
<td>0.712</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>-0.598</td>
<td>0.573</td>
<td>1.088</td>
<td>1</td>
<td>0.297</td>
<td>0.550</td>
<td>0.179</td>
</tr>
<tr>
<td><strong>Constant</strong></td>
<td>-0.287</td>
<td>2.255</td>
<td>0.016</td>
<td>1</td>
<td>0.899</td>
<td>0.750</td>
<td></td>
</tr>
</tbody>
</table>
2.5 Discussion

2.5.1 Nutritional status of CDAD group and hospital comparison groups
There was no statistical difference in MUST score between the CDAD group and the hospital comparison group indicating that both groups were at equal nutritional risk. However, a major limitation of this finding was that the groups were not matched for age and sex. The CDAD group were older females on medical wards, whereas the comparison group were younger and a greater percentage on surgical wards. Despite these factors the findings of this study indicate that the CDAD group have a high rate of malnutrition as defined by BMI. This is highlighted when compared to other data on malnutrition in one other group of CDAD patients and published Irish data of nutritional status in different hospital patient groups (table 2.5).

The high rate of malnutrition found in this CDAD patient group is supported when compared to the UK study of Wong et al., (2008). A comparable percentage of patients with CDAD in these studies were observed to be at risk of malnutrition. The UK study reported that 57% of their CDAD patients were at risk of malnutrition, a similar percentage to that observed in this Irish group of CDAD patients (58.8%). Further comparison of these two groups of CDAD patients with the BAPEN data on nutritional status of the general hospital population highlights that the prevalence of nutritional risk is nearly double in CDAD patients. Using MUST to determine malnutrition risk in the hospital setting, data from the 2010 NSW indicates that malnutrition risk was identified in 33% of patients admitted to hospital most of whom were at high risk of malnutrition (25%) with 8% at medium risk. Using these data, the authors estimated a ward prevalence of malnutrition as 39% (assuming there was no mortality and no “malnutrition” develops during the hospital stay) (Russell & Elia, 2011). Previous data from an Irish setting found a prevalence of malnutrition in
11% of medical and surgical patients on admission to two teaching hospitals (Corish et al., 2000). Both BMI and upper arm anthropometry were used to define undernutrition.

The use is of the MNA again highlighted that CDAD patients are a group at high risk of malnutrition as a similar number was classified at high risk by each screening tool. The MNA identified more patients in the CDAD group as at risk of malnutrition compared to MUST but this was difference was not statistically significant. There were discrepancies between the two screening tools in patients identified as being at risk; six patients classified as high risk using MUST were classified by the MNA as only being “at risk” (n = 4) or “normal” (n = 2). The MNA has been validated specifically for the elderly (Guigoz et al., 1996) and it may not be valid to use with these patients as both the CDAD and comparison patient groups included patients under 65 years of age. The usefulness of the MNA as a malnutrition screening tool in the acute setting could be questioned as it was originally validated for use in relatively healthy older people (Rasmussen et al., 2004) and, therefore, it may not be suitable for fraile older populations (Bauer et al., 2008b). Communication and comprehension deficits in some older people limit its usefulness with such patient groups and this factor was encountered in the study patient group. The MNA is thought to be most effective for nutritionally screening those aged over 65 living in the community, older residents in sub-acute care and those living in nursing homes (Bauer et al., 2008b). Despite its limitations in using the MNA observed in this study, the MNA is advocated as a nutritional screening tool particularly for use in the elderly. In this study similar findings for nutritional risk were obtained using both
methods. This supports the use of MUST as a screening tool able to identify nutritional risk in this patient group.

**Table 2.5 The nutritional status of the CDAD groups compared to other Irish nutritional status data.**

<table>
<thead>
<tr>
<th></th>
<th>CDAD group</th>
<th>Wong <em>et al.</em>, 2008</th>
<th>Corish <em>et al.</em>, 2000</th>
<th>BAPEN 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CDAD patients</td>
<td>Medical and surgical admissions</td>
<td>Nutrition Screening Week 2010</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>34</td>
<td>76</td>
<td>569</td>
<td>1527</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>21.0</td>
<td>--</td>
<td>--</td>
<td>26.3</td>
</tr>
<tr>
<td>&lt; 20 (%)</td>
<td>41.2</td>
<td>26</td>
<td>13.5</td>
<td>8</td>
</tr>
<tr>
<td>20-25 (%)</td>
<td>32.4</td>
<td>--</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>&gt; 25 (%)</td>
<td>26.5</td>
<td>--</td>
<td>46</td>
<td>60</td>
</tr>
<tr>
<td>MUST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0 (%)</td>
<td>23.5</td>
<td>--</td>
<td>--</td>
<td>67</td>
</tr>
<tr>
<td>Score 1 (%)</td>
<td>16.7</td>
<td>--</td>
<td>--</td>
<td>8</td>
</tr>
<tr>
<td>Score 2 or more (%)</td>
<td>58.8</td>
<td>57</td>
<td>--</td>
<td>25</td>
</tr>
</tbody>
</table>

-- data not provided/available

**2.5.2 Nutritional status of patients 65 years and older in CDAD and comparison groups**

As the two study groups were not controlled the CDAD group were an older group of hospitalised patients compared to the comparison group. It would be expected that those with CDAD would be older as older age is considered a risk factor for the acquisition of *C. difficile*. This was also supported in the regression analysis.
performed on the data. The variable age, was found to be the statistically significant variable in predicing the likelihood of having CDAD. In Ireland, the incidence of CDAD increases with age with those aged over 65 years at highest risk of infection (Health Protection Surveillance Centre, 2011). When those over 65 years of age in both groups were compared there was no statistical difference seen between weight, BMI and MUST score of these two groups. However, when the subjects over 65 years in the CDAD group are compared to Irish data of elderly populations, the high nutritional risk of the CDAD group is evident. True comparisons are very difficult to make as the patient groups were free living individuals, yet the vast contrast in BMI emphasises that those with CDAD are a very malnourished group. One Irish study reported that only 3% of healthy older people had a BMI lower than 20 kg/m$^2$ (Corish & Kennedy, 2003). More recent data on the Irish free-living population found that 1% of men and 2% of women over 65 years had a BMI less than 20 kg/m$^2$ (Morgan et al., 2008). In those aged between 18-64 years, only 0.3% of men and 1% of women had a BMI less than 18.5 kg/m$^2$; the mean BMI for men over 65 years was 28.1 kg/m$^2$ and women over 65 years was 27.3 kg/m$^2$ (Irish University Nutrition Alliance, 2011). The Irish Longitudinal Study on Aging (TILDA) published results of a national study of 8000 older people aged 50 years and older in May 2011. Three quarters of the subjects were overweight (44%) or obese (34%), only 1% of the population were underweight (BMI < 18.5 kg/m$^2$) (Barrett et al., 2011).

2.5.3 BMI
BMI is frequently quoted as an indicator of nutritional status and reflects chronic protein energy malnutrition. MUST and the Malnutrition Advisory Group of BAPEN use the lower boundary BMI value of 20 kg/m$^2$ to indicate the clinical risk of underweight; the risk becomes even greater below a BMI of 18.5 kg/m$^2$. These
cut-off values are based on physiological and clinical observations which show loss of body function as BMI decreases and the apparent normal body function in many older subjects with a BMI above 20 kg/m². RCTs of nutritional supplementation suggest benefits are more likely in older subjects with a BMI below 20 kg/m² with less benefit seen in those with a BMI over 20 kg/m² (Stratton et al., 2003). There is some debate over the appropriate level of BMI to define undernutrition, for example, WHO classifies normal or ideal BMI as 18.5 – 24.9 kg/m² (WHO, 1998) while BAPEN and the NICE guidelines consider that a BMI of between 18.5 and 20 kg/m² indicates possible risk of protein-energy malnutrition. If a BMI of <20 kg/m² was used as the sole determinant of malnutrition, a prevalence of malnutrition of 41.2 % in the CDAD group compared to 22.2% in the hospital comparison group would be observed. The rate of 41.2% is high when compared to other Irish data on the BMI of Irish hospitalised patients that was previously reported in a study carried out in two Dublin hospitals. This study found only 13.5% of a mixed group of medical and surgical patients had a BMI below 20 kg/m² (Corish et al., 2000) (Table 2.5). A true comparison is difficult, as the data in the older study was taken within 48 hours of the patient’s admission to hospital, whereas in this study population, the data were collected at various stages during hospital admission. In addition the percentage of patients with BMI <20 kg/m² in the study CDAD group is higher than the 26% with a BMI <20 kg/m² reported in the study by Wong et al., (2008). The high percentage of patients with low BMI’s perhaps indicates that the presence of chronic malnutrition is more common in patients with CDAD.

The differences observed in the BMI between the CDAD and comparison group could question the use of the MUST as the indicator of nutritional risk in this patient
group. There are a number of limitations of MUST, firstly MUST allows for the use of surrogate and self-reported measurements for weight, weight loss and height. The reliability and accuracy of these measurements can be questioned at the individual level and in some cases are relying on subjective criteria. In the elderly population in the presence of cognitive impairment it can be difficult and unreliable. In the CDAD patient group the majority of the data for recent weight loss was based on self-reported or estimated data rather than accurate measurements which could impact on the reliability of this information. In addition MUST assign equal weight to these three components of the tool (BMI, weight loss and oral intake). It could be questioned does a low BMI indicating chronic protein-energy malnutrition have a greater impact on outcome compared to recent weight loss or short term reduced oral intake in the CDAD patient group. However, it has been found BMI alone will not always detect patients at risk of malnutrition. As MUST take into consideration a BMI less than 20 kg/m$^2$ it will capture the chronically malnourished group as being at nutritional risk. As the majority of CDAD patients are the older population the surrogate measures for weight and height are often the only way to obtain data due to issues with mobility. In the CDAD patients there are a number of limitations when interpreting BMI. CDAD can result in manifestations of protein losing enteropathy involving ascites and peripheral oedema (Dansinger et al., 1996). Alterations in fluid balance, such as the presence of oedema, can make it difficult to accurately quantify the amount of excess extracellular fluid present. Although there are guidelines available to estimate body weight for the presence of excess fluid (Wicks & Madden, 1994) these only provide an approximation of oedema free body weight and lack precision. Future studies should consider if a low BMI is associated with in increased
risk of *C. difficile* acquisition and disease outcome. It would be useful measurement for the HPSC to collect in their surveillance data.

### 2.5.4 Identification of malnutrition in the patients with CDAD

The failure of nursing and medical staff to identify some patients in the CDAD group who were at nutritional risk highlights the concern that malnutrition is frequently not identified in healthcare facilities. This ongoing problem has been highlighted in the declaration released at the 2011 international conference “Fight Against Malnutrition – Two Decades On”. One of the four aims of the conference declaration is to improve the identification of malnutrition. The declaration is endorsed by the EU, Polish Society for Enteral and Parenteral Nutrition, ESPEN, European Nutrition for Health Alliance and the medical nutrition industry. The wide support for this declaration indicates that malnutrition and its identification is a major problem. In SVUH, there is a mandatory requirement to carry out MUST nutritional screening on each patient admitted. However, compliance with this requirement remains an issue. A hospital audit was carried out on 63 patient records on one day in February, March and April 2011. Completion of the screening tool ranged from 44-59% over the three day audit resulting in a number of medium and high risk patients who had not been identified on admission (Nutrition Committee SUVH, 2011). Despite the well-known medical and economic impact of malnutrition, it still remains unidentified in hospitalised patients. Previous Irish data showed that 40% of malnourished patients were referred for nutritional intervention (Corish *et al.*, 2000). Another study reported that of 40% patients at nutritional risk, only a small number had been identified and no nutritional plan or monitoring systems were in place (Rasmussen *et al.*, 2004). More recently, the presence of nutrition problems were observed in up to half the patients studied but these were only partly documented by
health care professionals. Clinical judgement was used to identify malnutrition in the majority of patients, BMI was not calculated and nutritional problems were not documented in many cases (Volkert et al., 2010). The previously discussed NSW 2010 data also highlights the difficulty that remains with nutritional screening and identification of malnutrition in Irish healthcare facilities. 72% of the hospitals did not have a nutritional screening policy and only 38% of the hospital audited nutritional screening (Russell & Elia, 2011). From the perspective of the study hospital the documented failure to identify high risk patients highlights the importance of the nutritional screening all patients. A comprehensive nutrition screening protocol will detect all patients at high nutritional risk and if implemented would have detected the six patients. Within any care setting there will always be groups of patients who are at greater nutritional risk than others. A universal policy of nutritional screening allows for all such patients to be detected and not only those thought to be “at risk”. The finding that nutritional supplements were being prescribed to patients that were not under the care of the dietetic service would warrant further investigation at a hospital level. The introduction of education about nutritional supplements to the relevant health care staff would be advisable to ensure appropriate supplements are being prescribed. Another option that may be the use of particular nutritional supplements being incorporated into care plans related to the nutritional screening tool.

2.5.5 Provision of probiotics to the CDAD group
Although this study had only a small patient sample, it does highlight that probiotics are being used in this patient group. However, the use of probiotics in patients with CDAD in SVUH was inconsistent in this study. Only 25% were prescribed probiotics and, among these, the dose of probiotics varied. No hospital-wide
guidance on the use of probiotics in CDAD or other conditions exists in SVUH. In addition the probiotic product supplied to patients contained *L. rhamnosus GG* for which there is no conclusive evidence to support its use as an adjunct to antibiotic therapy (Hickson, 2011).

### 2.5.6 Enteral nutrition and CDAD

In this study, only a small number of patients with CDAD were on ETF at the time they became infected with CDAD. It should be noted that the total sample size was small and that no patient had a gastrostomy in situ. It has previously been demonstrated that ETF is an independent risk factor for *C. difficile* colonisation (Simor *et al.*, 1993). Additionally post pyloric tube feeding significantly increases the risk for the development of CDAD in hospitalized patients (Bliss *et al.*, 1998). One study in a Dublin teaching hospital followed 73 subjects who developed CDAD through their hospital admission. Of these, 4.1% of patients were on PN and 30.1% were receiving nutrition via a NGT or PEG. NGT insertion/feeding were associated with more severe disease. However, this association was not statistically significant (Kyne *et al.*, 1999).

### 2.5.7 Future considerations for patients with CDAD

The purpose of this study design was to assess the nutritional risk as the time of CDAD diagnosis. From extrapolation of the literature describing the effects of infection it is commonly believed that CDAD is both a cause and effect of malnutrition. However no literature specific to CDAD is available to support this hypothesis. As this was an observational study whose primary outcome was the MUST score of patients only limited data on the other factors associated with CDAD development were collected. Accurate testing of the hypothesis that malnutrition contributed to the likelihood of CDAD acquisition was not the primary outcome of
the study and cannot be determined retrospectively as it would require the availability of data on all possible contributors to malnutrition before a causal relationship could be determined. Future work should look at above hypothesis as well as the impact of CDAD on a patient’s nutritional status.

It is well established that nutritional status declines during hospital admission (Braunschweig et al., 2000; Corish et al., 2000; Rasmussen et al., 2004). The Dublin study of 73 subjects who developed CDAD during their hospital admission mentioned previously classified 12.3% of their subjects as malnourished, defining malnutrition as weight loss of greater than 10% of body weight. However, no anthropometric data were provided at initial diagnosis of the disease (Kyne et al., 1999). Another significant factor for malnutrition risk in this patient group is diarrhoea. Diarrhoea is most commonly defined as a minimum of three liquid stools per day (WHO, 2005). It is characterized as a symptom of a disease in which the large or small intestine becomes irritated and this results in rapid movement of faecal matter through the large intestine. Diarrhoea leads to poor absorption of nutrients due to the rapid transit in the gut, deterioration of the absorptive mucosa and loss of specific transporters. It may produce a secretory state in the small intestine, preventing or reducing net absorption. Many studies have shown that there is evidence of carbohydrate malabsorption with diarrhoea with several focusing on the disaccharide lactose as the enzyme lactase, responsible for lactose digestion, can be reduced in enteric infection (Duggan & Nurko, 1997). Undigested carbohydrate may draw fluid from the intestinal lumen due to osmosis (Duggan & Nurko, 1997). Fat malabsorption may increase severity of the diarrhoea due to fatty acid induced colonic secretions (MacLean et al., 1978). A study of faecal output and nitrogen
content over a 24-hour period in eleven patients with CDAD reported a mean faecal nitrogen loss was 38 mg/kg/body weight/day. The authors recommended that faecal nitrogen loss should be considered in nitrogen balance studies in these patients (Tayek et al., 1987). Loss of nutrients may also increase during diarrhoeal disease of bacterial origin. Cellular debris increases, intestinal flora proliferates and undigested solids may adsorb minerals including zinc and reduce their bioavailability.

If diarrhoea is persistent (usually classified as lasting more than 14 days), this will have severe medical and nutritional implications (WHO, 1988). A close association between diarrhoea and malnutrition is documented in the literature (Checkley et al., 2008) with general acceptance that poor nutritional status, as assessed by anthropometric measurements, leads to greater risk of diarrhoea (Chowdhury et al., 1990; Checkley et al., 2002) and that pre-existing malnutrition is associated with increased severity of diarrhoeal disease. If left untreated, diarrhoea-induced malnutrition can increase morbidity.

A further aspect of the pathophysiology of malnutrition is the disease process itself. In recent years, there is a greater understanding that a combination of under - or overnutrition associated with acute or chronic inflammation from the disease state leads to altered body function and will worsen nutritional status (Jensen et al., 2010). The clinical manifestations of CDAD result in systemic symptoms such as fever, anorexia, nausea and malaise. Leucocytosis, raised C-reactive protein and low albumin levels are frequently seen. Infection impairs nutritional status and body composition in a number of ways. Firstly, infection is characterised by anorexia and can range from as little as 5% to almost complete loss of appetite (Yaqoob & Calder, 2003). This will promote loss of lean tissue if nutritional intake is inadequate.
Infection is also associated with increased basal metabolic rate during fever. Each one degree in body temperature is associated with a 13% increase in metabolic rate which in turn increases energy requirements. The infection itself can result in nutrient loss and malabsorption. In CDAD, as previously discussed, the symptoms of the disease can result in malabsorption and nutrient losses. A further consequence of inflammation as a result of the disease is altered metabolism and redistribution of nutrients. This is a result of the production of proinflammatory cytokines and immunoglobulins by leucocytes. The synthesis of these acute phase protein results in the loss of amino acids from skeletal and muscle tissues (Yaqoob & Calder, 2003).

Each of these factors impact on a patient’s nutritional status, including those identified as being at low nutritional risk at initial nutritional screening. This highlights the need for nutritional screening to be carried out at regular intervals.

2.5.8 Limitations
There are two main limitations of this study. Firstly is the small sample size so, interpretation of the results must be with caution. An additional criticism which was previously discussed was that the hospital comparison group was not matched to the CDAD group. As the hospital comparison group patients selected in this study came from patients on both medical and surgical wards who were at different time points in their admission, it was anticipated that the patient group would reasonably accurately reflect the nutritional status and malnutrition risk of the general hospital patient. Many advantages and disadvantages of matching are quoted in the literature. Matching controls for confounding variables can be relevant when there is a substantial difference in the occurrence of possible confounders between cases and controls. Matching can increase a study’s effectiveness by forcing case and controls
to have a similar distribution across confounding variables (Rose & van der Lann, 2009). However, matching may introduce bias, as when trying to match the cases with controls, some of the cases may be excluded as they cannot be matched. This will therefore create a sample of cases that is not a true representative of the study population. The variables chosen to match are very important. If the controls are matched to cases based on a variable that is not a true confounder, this can impact on the study’s accuracy (Rose & van der Lann, 2009). However, the failure to control for age and sex in this study may be the reason why no difference was seen between the MUST score in the two groups. There was a trend towards more females and more medical patients in the CDAD group.

2.6 Conclusion
Despite the lack of a significant difference in the prevalence of nutritional risk as determined by MUST between patients with CDAD and the other hospital group, this study highlights that those with CDAD are at high risk of malnutrition. The data also indicate that these patients are older, female and have a lower BMI perhaps implying that they are more likely to be chronically malnourished. Both the groups studied had a similar prevalence of nutritional risk, however it is clear irrespective of the method used to ascertain nutrition risk that those patients with CDAD are at higher risk of malnutrition.

The study assessed malnutrition only at time of diagnosis and further study as to the effect of the disease on the nutritional status of patients with CDAD is warranted.
CHAPTER 3 - Dietitians’ opinions and use of probiotics in CDAD and enteral feeding practices in CDAD
3.1 Introduction
As CDAD is a disease associated with altered GIT microflora, the idea that probiotics may play some role in preventing the development or recurrence of the disease is very appealing. The mechanisms of action of probiotics imply that there are a number of ways that both bacterial and yeast probiotics could be of benefit in CDAD. Over the past few decades, a number of probiotics have been investigated for their effectiveness in the primary prevention of CDAD, the prevention of AAD and subsequent development of CDAD as a secondary outcome, and prevention of recurrence of CDAD. Unfortunately, the results of these studies remain inconclusive.

Dietitians are one of the healthcare professionals involved in the care of patients with CDAD in both hospital and community settings. As a result of increased availability, consumer awareness and use of probiotic products, dietitians are often asked for advice on these products. It is vital that dietitians understand fully the scientific basis of FF claims, including probiotics, as they are the healthcare professional with primary responsibility for nutrition education and medical nutrition therapy (Anderson et al., 1998). Information on dietitians’ opinions about probiotics and the recommendations they currently make on their use in dietetic professional practice has not been previously reported. To gather this information, a questionnaire was designed to assess Irish dietitians’ opinions about probiotics and the recommendations they currently make on the use of these products in a number of clinical conditions, but with a specific focus on CDAD.
3.2 Aims

The aims of this study were to:

- Investigate Irish dietitians’ beliefs and recommendations regarding probiotics in patients with CDAD and other clinical conditions;
- Obtain data on the probiotic products and strains currently in use in Irish healthcare facilities and assess the factors determining use of these products and if guidance on their use exists;
- Assess the current enteral feeding practices of dietitians in patients with CDAD.
3.3 Methodology

3.3.1 Participants
A self-completed questionnaire was chosen as the most appropriate research tool to facilitate access to dietitians working in a range of professional settings and varied geographical locations within the Republic of Ireland (ROI). When this study was undertaken, there were 550 members of the Irish Nutrition and Dietetic Institute (INDI) with ROI addresses; each was sent a postal questionnaire.

The study design and methodology was approved by the ethics committee of the Dublin Institute of Technology (DIT). Permission to access its members was approved by the executive council of the Irish professional body for dietitians, the INDI.

3.3.2 Study questionnaire
The study questionnaire consisted of five pages and included an introductory page explaining the background and rationale to the research (Appendix 8). The questionnaire was divided into four sections and consisted of a combination of 26 closed and open questions. Advantages to closed questions are that they are specific, provide the same frame of reference for all respondents and allow for quantitative analysis (Wall et al., 2002). Disadvantages to closed questions are they can limit the depth of participant response and consequently data collection (Bowling, 2009). Open questions are often difficult to define, neither being strictly qualitative nor quantitative, but can capture and identify issues that were not taken into consideration in the closed questions (O'Cathain & Thomas, 2004).
3.3.2.1 Demographic and professional data
Data on gender, place of employment, size of dietetic department in place of work, number of years qualified, work setting and patient specialty were collected.

3.3.2.2 Dietitians’ opinions
Participants were asked if they believed probiotics had a role in the prevention and treatment of CDAD. They were also asked if they recommend probiotics in their clinical practice. A list of six clinical areas in which some studies have shown positive results for probiotic use was included in the questionnaire. Participants were asked if they recommend probiotics in these conditions. The names of other clinical conditions in which they recommend probiotics were requested.

3.3.2.3 Provision of probiotics in the clinical setting
This section of the study questionnaire asked if the healthcare facilities in which the participating dietitians worked provided probiotics to patients/clients and, if so, were policies or guidelines on the use of probiotics available for some or all conditions in which they were used. Participants were also asked to identify the form, strain and brand of probiotic used in the healthcare facility in which they worked, and what factor(s) determine the probiotic(s) products used. Current practice in recommending the use of probiotics in the prevention or treatment of CDAD was ascertained, specifically dietitians’ recommendations for probiotic use in patients prescribed antibiotics, and those with CDAD or non-CDAD diarrhoea. Dietetic recommendations for vitamin and mineral supplementation in patients with CDAD were also elicited.
3.3.2.4 Enteral feeding, CDAD and probiotics
The fourth section requested information about dietitians’ practices using probiotics in patients fed via enteral tubes and the enteral feeds most commonly recommended for patients with CDAD.

3.3.2.5 Pilot questionnaire
The survey questionnaire was piloted among dietitians (n = 11) working in one nutrition and dietetics department in an acute academic teaching hospital to ensure that the questions asked could be clearly understood and that the directions for answering the questions were unambiguous. Piloting of questionnaires ensures that questions are worded clearly and they are appropriate for the target population (Wall et al., 2002). Following the pilot study, changes were made to some of the questions. The option of “do not know” as an answer in the questions about dietitians’ opinions was included [questions: 2 (a) and 2 (b)]. The wording of the question was changed to reflect that dietitians recommend probiotics rather than the dietitian administering probiotics to patients [questions: 3 (l), 3 (m), 4 (a) and 4 (b)].

3.3.3 Data collection
In order to maximise the response rate to the postal questionnaire, the recommendations in the systematic review on the topic by Edwards et al., (2009) were followed. A stamped addressed envelope was included with each questionnaire to make responding easier. A prize was offered to participants as an incentive to respond. A further call for participation offering an online method of response was also offered.

In order to identify the winner of the prize, the questionnaires were coded. These identification codes were removed once the data were collected. A request for
further participation in the study was made using the INDI newsletter. This offered an opportunity to respond to the questionnaire online up to four weeks after the initial closing date with the aim of increasing the response rate.

3.3.4 Statistical analysis
A codebook was prepared. Each question in the questionnaire was given a unique variable name, and numbers were assigned to each of the possible responses to each question. For the three open ended questions, the responses were reviewed and common themes identified. Six themes were identified and assigned a numerical code and a further numerical code was assigned to those responses that did not fall into the six themes. A data file was created following the format of the codebook using Microsoft Excel (version 2007) database (Microsoft Corporation, Redmond, Washington). The data set was then transferred to the Statistical Package for Social Sciences (SPSS) for Windows Version 19 (IMB, SPSS Statistics, United States) for analysis. Prior to analysis being performed, the data were checked for errors. All the variables in the data set were categorical variables and checked by reviewing the descriptive statistics. The minimum, maximum, number of valid and missing cases were reviewed to ensure that all values were within the possible values for that variable (Pallant, 2007). Once the data file contained no errors, descriptive statistics were used to describe the dataset. As all the variables were categorical, frequency of occurrence was used to describe the study variables. In the analysis of the questions regarding use of probiotics in practice, the responses from dietitians working in the “other category” were excluded. Many of these were not working directly with patients/clients and therefore probiotic use was not applicable. Chi-squared tests were performed to investigate differences between the opinions and the practices of dietitians who worked in the hospital setting compared to the community setting and
for differences between more and less experienced dietitians. For comparison of the use of probiotics among dietitians, dietitians who responded that the use of probiotics was not applicable to their practice were excluded from analysis. Due to the small number of dietitians with greater than 25 years or less than one year professional experience, age was grouped into three categories (less than one year to five years experience, five to fifteen years experience and greater than sixteen years experience). In cases where the lowest frequency in a cell was less than five Fisher’s Exact Probability Test was used instead. Statistical significance was set at a probability of less than 5% (p < 0.05).
3.4 Results

3.4.1 Response rate
There was a 40.9% (225/550) response rate to the questionnaire. All responses were returned via the postal method, there were no responses via the additional online method that had been offered. Eleven responses were excluded from statistical analysis as they were returned by student or transition members of the INDI (n = 2), retired or non-practicing members (n = 4), questionnaire was not applicable to current work (n = 3) or contained incomplete information (n = 2). Therefore, of the 225 questionnaires returned, 214 were included in the analysis.

3.4.2 Participant characteristics
Forty-three hospitals were represented by the questionnaire responses. These included responses from 10 academic teaching hospitals and from hospitals within each of the four Health Service Executive (HSE) areas. Responses were received from six private hospitals and from one hospital in the United Kingdom (Appendix 9).

Each of the four HSE areas was represented by responses from the community setting, with the largest response from the Dublin Mid-Leinster region. Of those employed in the community, 75.6% (n = 31) worked in primary care, 22% (n = 9) had a mixed case load and worked in both health promotion and primary care and 2.4% (n = 1) worked only in health promotion.

The employment in the ‘other’ category was private practice (n = 8), consultancy (n = 1), industry (n = 2), charity (n = 1), education (n = 2), research (n = 1) and other HSE organisations (n = 3).
In each category, the majority (47.7%; n = 102) of dietitians had six to 15 years experience and worked with adults (79.3%; n = 158). Many treated both medical and surgical patients. There was a subgroup of hospital dietitians who identified part or all of their case load as working in critical care (n = 18). The demographic and professional characteristics of the respondents are described in Table 3.1.
Table 3.1 Demographic and professional characteristics of dietitians (n =214)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>212(99)</td>
</tr>
<tr>
<td>Male</td>
<td>2(1)</td>
</tr>
<tr>
<td><strong>Place of employment</strong></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>155(72.4)</td>
</tr>
<tr>
<td>Community</td>
<td>41(19.2)</td>
</tr>
<tr>
<td>Other</td>
<td>18(8.4)</td>
</tr>
<tr>
<td><strong>Years qualified as a dietitian</strong></td>
<td></td>
</tr>
<tr>
<td>Less than 1 year</td>
<td>4(1.9)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>67(31.3)</td>
</tr>
<tr>
<td>6 to 15 years</td>
<td>103(48.8)</td>
</tr>
<tr>
<td>16-25 years</td>
<td>28(13.1)</td>
</tr>
<tr>
<td>Greater than 25 years</td>
<td>12(5.6)</td>
</tr>
<tr>
<td><strong>Patients worked with</strong></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>158(79.3)</td>
</tr>
<tr>
<td>Paediatrics</td>
<td>31(14.5)</td>
</tr>
<tr>
<td>Both adults and paediatrics</td>
<td>23(10.7)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>2(0.9)</td>
</tr>
</tbody>
</table>
3.4.3 Dietitians’ opinions about probiotics in the prevention and treatment of CDAD

There was no consensus among dietitians about the role of probiotics in both the treatment and prevention of CDAD (Table 3.2). More than half (52.8%) responded that they did not know if there was a role for probiotics in the prevention of CDAD whereas almost two-thirds believed that they could play a role in the treatment of CDAD (Table 3.2). There was no significant difference in the opinions of dietitians working in community and hospital settings on the role of probiotics in the prevention (p = 0.285) or treatment of CDAD (p = 0.680). There was also no relationship between dietitians’ opinions about probiotics in the prevention (p = 0.119) or treatment of CDAD (p = 0.107) and the number of years qualified.

Additional comments were made by respondents about the role of probiotics in the prevention of CDAD (n = 116) and their role in the treatment of CDAD (n = 124). In the prevention of CDAD, a similar proportion commented on the positive scientific evidence (19.8%; 23/116) as those who thought the scientific evidence was lacking or inconclusive (18.1%; 21/116). One individual had positive experiences with probiotics in preventing CDAD; however; 20.3% (24/116) commented on their lack of experience or knowledge in the area. Of those who supported the use of probiotics in the prevention of CDAD, the proposed mechanisms of action of probiotics were mentioned by 29.3% (34/116).

Similar themes emerged in response to the use of probiotics for the treatment of CDAD. The positive evidence for a role for probiotics in treatment was mentioned by 29% (36/124) and the mechanism of action of probiotics in the treatment of CDAD by 29% (36/124). For those who did not know or who did not believe that probiotics had a role in the treatment of CDAD, the negative scientific evidence
(30/124) or their own lack of experience (12/124) was quoted. More dietitians reported positive personal experience in the use of probiotics in the treatment of CDAD (5/124). A small number of respondents commented that a number of other factors (5/124) such as the medical team or the patients influenced the use of probiotics.

Table 3.2 Dietitians’ opinions on the role of probiotics in the prevention and treatment of CDAD (n = 214)

<table>
<thead>
<tr>
<th>Dietitians’ response</th>
<th>Role of probiotics in the prevention of CDAD (%)</th>
<th>Role of probiotics in the treatment of CDAD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Believe probiotics have a role</td>
<td>33.6</td>
<td>65.4</td>
</tr>
<tr>
<td>Do not believe probiotics have a role</td>
<td>13.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Do not know if probiotics have a role</td>
<td>52.8</td>
<td>30.9</td>
</tr>
<tr>
<td>Not applicable to dietetic practice</td>
<td>10.7</td>
<td>10.7</td>
</tr>
</tbody>
</table>

3.4.4 Recommendations for probiotics in the prevention and treatment of CDAD

Most (65%) dietitians do not use probiotics for the prevention of CDAD although almost two-thirds use them for the treatment of CDAD. Practice among those using probiotics for the treatment of CDAD varies (Table 3.3). There was no statistical difference between years qualified and use of probiotics in the prevention of CDAD (p = 0.285) or treatment of CDAD (p = 0.73). There was also no statistical difference between dietitians working in community or hospital settings in their use
of probiotics for the prevention of CDAD ($p = 0.581$) and their use of probiotics for the treatment of CDAD ($p = 0.45$).

**Table 3.3 Dietitians’ use of probiotics in the prevention and treatment of CDAD (n = 196)**

<table>
<thead>
<tr>
<th>Dietitians’ response</th>
<th>Use of probiotics in the prevention of CDAD (%)</th>
<th>Use of probiotics in the treatment of CDAD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always use probiotics</td>
<td>9.8</td>
<td>36.4</td>
</tr>
<tr>
<td>Never use probiotics</td>
<td>65.0</td>
<td>27.6</td>
</tr>
<tr>
<td>Occasionally use probiotics</td>
<td>14.5</td>
<td>25.2</td>
</tr>
<tr>
<td>Not applicable to practice</td>
<td>10.7</td>
<td>10.7</td>
</tr>
</tbody>
</table>

**3.4.5 Dietitians’ recommendations for the use of probiotics in other clinical conditions**

Thirty-three (15.4%) respondents would never recommend probiotics in their clinical practice. There was no association between those who recommend probiotics and years qualified ($p = 0.390$). Of those who recommend probiotics (84.6%), this was most frequently for the management of irritable bowel syndrome (IBS) (82.3%, n = 149). The use of probiotics in the other five clinical conditions that were provided as options for the dietitians is illustrated in Figure 3.1. Respondents also provided other conditions for which they would recommend probiotics. Antibiotic treatment and
antibiotic-associated diarrhoea were conditions in which probiotics were recommended most often. Dietitians also reported recommending probiotics for the treatment of thrush, diarrhoea, diverticular disease, constipation, radiation enteritis, cystic fibrosis, pouchitis, autism, sports nutrition, on an individual basis, gastrointestinal distension, malnutrition and acute diarrhoea in children.

3.4.5.1 Probiotic use by dietitians with non-\textit{Clostridium difficile} diarrhoea

There is variation in the use of probiotics in patients with diarrhoea that is not due to \textit{C. difficile}. Forty two percent (n= 82) of dietitians working in hospital and community settings stated that they would occasionally use probiotics when a patient develops diarrhoea while on antibiotics in the absence of \textit{C. difficile} toxins. When diarrhoea occurs, \textit{C. difficile} is not isolated and the patient is not on antibiotics,
40.8% of dietitians would recommend the use of probiotics whereas 34.7% would never recommend them in this situation.

3.4.6 Probiotic provision and guidance in healthcare facilities

3.4.6.1 Commencement of probiotics
In the hospital and community setting, respondents indentified “dietitians” as the healthcare professional most likely to recommend the commencement of probiotics in patients with CDAD. They also indicated that medical staff are the healthcare professional group next most likely to recommend the administration of probiotics to patients (Figure 3.2).

Figure 3.2 Dietitians' opinion on the healthcare professional to recommend the commencement of probiotics (n=196)
3.4.6.2 **Probiotic products supplied by healthcare facilities**

To establish the probiotic products supplied by healthcare facilities, only the responses from hospital dietitians were analysed (n = 155) as probiotics are not supplied to patients within the community. Of the 43 hospitals, 93% (n = 40) buy probiotic products for provision to patients. Two hospitals no longer provide probiotics for financial reasons and the dietitian in one hospital (maternity) reported that probiotics are never used.

Eleven different products were reported as available for patients (Appendix 10). There were some inconsistencies between dietitians working in individual hospitals as to the products available. Overall, it was evident that the yogurt drink “Everybody” (Yoplait franchise produced by Glanbia plc Consumer Foods Division, Dublin) was the most commonly available commercial product. This product contains the probiotic strain *L. rhamnosus* GG. The factors influencing the probiotic supplied within hospitals were catering department choice (40.7%; n = 63) and clinical evidence for the product supplied (16.8%; n = 26). Twenty dietitians (12.9%) reported that a combination of both factors mentioned above determined the product supplied. Despite over half the dietitians surveyed reporting that clinical evidence for the product influenced the product supplied, almost half (48.4%; n = 75) did not know the strain present in the products used.

3.4.6.3 **Guidelines/policies on the use of probiotics**

To establish if there is guidance available to dietitians on their use of probiotics, the study questionnaire investigated the existence of policies or guidelines in this area. Responses from dietitians working in hospital and community settings only were analysed (n = 196). Of these, 4.1% (n = 8) responded they had a policy or guideline
in their place of work for the use of probiotics while 4.6 % (n = 9) responded they had a policy or guideline in their place of work for the use of probiotics in CDAD. The response to this question varied within individual hospital and community settings, indicating that in those settings where a policy exists, not all staff were aware of its existence. Among the additional comments provided by respondents (n =55) at the end of the questionnaire, 21.8% (n =12) identified the need for policies or guidance on probiotic use.

3.4.7 Enteral nutrition and CDAD
No standardardisation of practice was observed among dietitians in the use of probiotics with enteral tube feeding (Figure 3.3). Approximately one-third of dietitians (30.6%) reported recommending the use of probiotics occasionally in patients with CDAD who were being enterally fed and a similar proportion (36.2%) recommended their use in other clinical conditions when enteral nutrition was required. There was no statistical association between the place of work (p = 0.229) or years practicing (p = 0.340) and the use of probiotics in ETF patients with CDAD. Neither was an association seen between the use of probiotics in ETF in other conditions and dietitians’ place of work or years of experience. The enteral feed most commonly used in patients with CDAD by the majority of dietitians was a polymeric feed (79.6%); few dietitians recommended the use of semi-elemental (7.1%) or elemental (0.5%) feeds. There was no consensus on the provision of dietary fibre to patients with CDAD; 31.6% provide no fibre to patients with CDAD, 27% use a mixture of a non-fibre containing feed with a fibre containing feed, while only 17.9% stated that they would always recommend a fibre-containing feed.
3.4.8 Vitamin and mineral supplementation and CDAD

The majority of dietitians (57.9%) reported recommending vitamin and mineral supplementation during an episode of CDAD if warranted by the patient’s nutritional status, while 17.3% consider both diagnosis and nutritional status when deciding whether to recommend additional vitamin and minerals. Only one dietitian reported routinely recommending a vitamin and mineral supplement in patients who develop CDAD.
3.5 Discussion
In recent years, there has been a greater awareness of the potential role of probiotics with the emerging evidence of their efficacy in some human diseases, and the increased availability of probiotic products to consumers. Dietitians are key healthcare professionals who can influence the use of probiotics both among consumers and other healthcare professionals. There are a number of studies investigating dietitians’ attitudes towards FF (Lee et al., 2000; de Jong et al., 2004; McConnon et al., 2004; Landstrom et al., 2007b). In the studies by Lee et al., (2000) and Landstrom et al., (2007b) dietitians’ opinions of FF were investigated. The authors did not differentiate between dietitians’ opinions about different FF. This is the first study that has examined dietitians’ beliefs or attitudes towards probiotics alone, specifically in relation to their professional practice. It also highlights some aspects of dietetic professional practice currently taking place in the ROI.

3.5.1 Response rate
The response rate of 40.9% was lower than anticipated and has the potential to introduce some bias to the results, as non-responders can undermine study validity and thus generalisability to a wider population (Cook et al., 2009). A response rate of 75% is considered ideal (Bowling, 2009); however, response rates to all types of surveys have been declining (Bowling, 2005), especially among healthcare professionals. This has been attributed to an increased demand to participate in research activities (Cook et al., 2009). Cook et al., (2009) showed that the average response rate to postal surveys among healthcare professionals was 56% (in studies published from 1996-2005). Only 16% of the studies analysed achieved a response rate of 75% or over. In the literature, response rates for postal surveys of dietitians
have been between 46.8 and 53% (Cashman et al., 2003; Mackel et al., 2003; de Jong et al., 2004). An online web survey conducted by another Irish dietitian on the topic of professional development at the same time and to the same group of dietitians had a similar response rate (43.7%) (Fitzpatrick, 2010).

3.5.2 Participants
The employment profile of the study participants was similar to that obtained from the INDI workforce planning survey of clinical nutritionist/dietitians undertaken in May 2010 (INDI, 2010). This showed that 72% of dietitians were employed in public and private hospitals and 28% in the community setting. It is, possible that dietitians with greater experience of managing CDAD were more likely to complete the questionnaire. As 73% of CDAD cases in Ireland occur in hospitals (HPSC, 2010); this may have resulted in the higher response rate from dietitians working in that setting. Additionally, CDAD is more commonly seen in adults and older persons which may account for the lower response from dietitians working in the paediatric setting.

3.5.3 Dietitians’ use and opinions of probiotics and CDAD
There is no consensus among Irish dietitians on the role and use of probiotics in the prevention and treatment of CDAD with more than half of all dietitians surveyed (52.8%) reporting that they did not know if there is a role for probiotics in the prevention of CDAD. There was greater support (65.4%) for a role for probiotics in the treatment of CDAD. As might be expected, given the number of dietitians who did not know if there was a role for probiotics in the prevention of CDAD, the majority do not recommend probiotics for its prevention. In the treatment of CDAD, no consensus on the practice of recommending probiotics was evident. Some dietitians recommended probiotics occasionally, and some in all cases, to prevent
and/or treat CDAD. This is despite the lack of published evidence to support the use of probiotics in the treatment of CDAD. Although there appears to be a possible role for use of the probiotic *S. boulardii* in conjunction with high dose vancomycin in the prevention of CDAD recurrence (McFarland *et al.*, 1994; Surawicz *et al.*, 2000), randomised double-blind placebo trials of sufficient size to detect significant differences are still lacking. Currently, this yeast is not being used as a probiotic in Irish hospitals.

The treatment guidance document for CDAD from the ESCMID (Bauer *et al.*, 2009) states that there is insufficient evidence to recommend probiotics in addition to antibiotics for the treatment of CDAD. The guidelines make reference to safety issues that have been reported with *S. boulardii* (Bassetti *et al.*, 1998; Munoz *et al.*, 2005) and the increased mortality observed in a study when probiotics were used in a RCT in patients with acute pancreatitis (Besselink *et al.*, 2004). The UK guidelines from the Health Protection Agency & Department of Health (2008) also comment on the use of probiotics in CDAD. They currently do not recommend probiotics to prevent CDAD due to the lack of statistical significance in two meta-analyses by Dendukuri *et al.*, (2005) and Pillai & Nelson (2008). US clinical practice guidelines also do not recommend the administration of probiotics to prevent primary CDAD. This is due to the lack of evidence and the potential risk of blood stream infection from probiotic use (Cohen *et al.*, 2010). There is also no support for the routine use of probiotics from the Australasian Society for Infectious Diseases; again this is based on the lack of efficacy and the potential for adverse events reported in the scientific literature (Cheng *et al.*, 2011).

Irish dietetic practice should follow the guidance provided by the review document ‘Surveillance, Diagnosis and Management of *Clostridium difficile* in Ireland (HPSC,
2008). Following their review of the evidence on probiotics, the HPSC concluded that the routine use of probiotics cannot be recommended. Probiotics should not be used either in the prevention or treatment of CDAD until there is more conclusive evidence for their use. Moreover, the specific probiotics currently used to prevent or treat CDAD in Irish health care facilities have even less evidence for their use than those referred to in the studies above.

3.5.4 Dietitians’ recommendations for probiotic use
Only 15.4% of dietitians never recommend the use of probiotics in their practice. In those recommending probiotics, IBS was the most common condition for which they were recommended (by 81.4%). These findings are comparable to those of US gastroenterologists; the majority (98%) of gastroenterologists supported the use of probiotics in patients with IBS (Williams et al., 2010). The symptoms of IBS are thought to be due to bacterial overgrowth in the small intestine causing increased fermentation and gas production (Wilhelm et al., 2008). The most commonly studied probiotics in IBS are Lactobacillus, Bifidobacterium and the mixture probiotic product VSL#3 (Williams, 2010). The NICE guidelines on the management of IBS, published in 2008, reviewed thirteen studies that met their inclusion criteria and concluded that probiotics are effective in some people with IBS but not in all. When products were from reputable sources, no harm was identified from the ingestion of probiotics. The NICE guidelines conclude with the recommendation that ‘people with IBS who choose to try probiotics should be advised to take the product for at least four weeks while monitoring the effect. Probiotics should be taken at the dose recommended by the manufacturer’ (NICE, 2008). A systematic review on the use of probiotics in IBS conducted by Moayyedi et al., (2010) which included 18 papers with 1650 participants concluded that
probiotics had a statistical effect in reducing IBS symptoms, but that there was no
difference in the different types of probiotics used, all of them showing a trend
towards benefit. The main limitation acknowledged in this review was the number
of different probiotic strains and doses used in the studies reviewed and therefore no
recommendation on the best probiotic and dose for the treatment of IBS were made.
This limitation has been reiterated by other authors investigating this topic
(Williams, 2010).

For more specific evidence and guidance for the dietetic profession, the British
Dietetic Association (BDA) gastroenterology specialist group developed UK
evidenced-based practice guidelines for the dietetic management of IBS in adults.
Their inclusion criteria were studies that used probiotic products that are available to
consumers in the UK. Of the five studies identified, the results were too weak to
support the therapeutic use of probiotics in IBS. They advised that interventions
using probiotics to further improve IBS symptoms can be considered within second
line dietary treatment. As with other reviews and guidelines, there was insufficient
evidence to recommend a specific probiotic. The dietetic practice guideline
recommended that patients should be advised that some products in probiotics may
increase IBS symptoms, that the long term effects of probiotics are unknown and that
if there is no improvement with one probiotic product, another one may need to be
tried (Mc Kenzie et al., 2010). It would seem reasonable for Irish dietitians to
recommend probiotics for IBS patients in a manner similar to that of UK dietitians.
However, specific guidance on probiotic products available on the Irish market
would be useful for practicing dietitians.
The lack of support for probiotics in the management of the paediatric condition, necrotising enterocolitis (NEC), may be explained by the low response rate from dietitians who work with children and, that even within paediatrics, the management of NEC is a specialist area.

### 3.5.5 Use of probiotics in other clinical conditions

A number of other clinical conditions in which this group of dietitians would recommend probiotics were cited. Antibiotic treatment and antibiotic-associated diarrhoea were the most common situations in which probiotics would be suggested (by 12% and 8.7% of dietitians respectively). In comparison probiotics were recommended by 21% Dutch dietitians, for those with recent diarrhoea and after antibiotic treatment (de Jong et al., 2004). This study investigated FF in general rather than probiotics specifically, and so contained limited detail on products used and doses recommended. In a study of New Zealand GPs (n = 45), probiotics were mostly commonly recommended for diarrhoea (44.4%) (Schultz et al., 2011). However, there was no information given on the cause(s) of diarrhoea in this study.

AAD is a common problem, occurring in 5-25% of patients receiving antibiotics, although the rates reported depend on the antibiotics used and the population studied (Bartlett, 2002). Probiotics given in conjunction with antibiotics for the prevention of AAD have been extensively studied in both children and adults. Several systematic reviews document that most of the probiotics tested have been shown to be effective in reducing risk of AAD in the general population (Cremonin et al., 2002; D’Souza et al., 2002; Hawrelak et al., 2005; Szajewska & Mrukowicz, 2005). *L. rhamnosus* GG and *S. boulardii* are documented as being most efficacious. These are the strains which have been most commonly used in the studies. From a review of all studies, it can be concluded that the results of studies using probiotics to reduce AAD are
promising but that conclusive evidence is still lacking, additionally it cannot be stated that all probiotic strains are effective (McFarland, 2009) Again the findings from this study show that this group of dietitian are using probiotics in an area where the evidence does not fully support their use.

3.5.6 Probiotics supplied in hospitals/ healthcare facilities and guidance around probiotic use
From this questionnaire it is evident that probiotics are being provided to patients in the majority of hospitals and other health care facilities in Ireland. The dietitians have identified themselves as the primary healthcare professional to recommend probiotics in CDAD. Similarly, in a randomly selected group of Canadian dietitians, 81% (n = 122) they too believed that dietitians were the most appropriate professional to recommend FF (Sheeshka & Lacroix, 2008). Such beliefs mean that dietitians should have a good knowledge of FF, the probiotic products provided in healthcare facilities and also the evidence for their use. The dietitians surveyed in this study had poor knowledge of the probiotic strains in the products they supplied or recommended. Around half (47.7%) could not identify even one strain present in the product supplied. The catering departments of healthcare facilities were also reported to have the biggest influence on the probiotic supplied. One issue that is very clear from the studies carried out with probiotics in the treatment of various clinical conditions is that the positive effect is dose and strain dependent. The administration of a probiotic product that may only contain one strain to a diverse hospital population could be described as futile. The limited knowledge of dietitians of the strains being used, despite them taking responsibility for recommending probiotics, identifies a deficit in knowledge and professional practice.
The presence of policies or guidelines on the administration of probiotics within clinical settings appeared to be unclear, with disagreement within departments as to the existence of guidelines. Analysis of the practices of dietitians working in specific areas was not possible due to the mixed caseloads of many dietitians. However, a sub-group of 18 (8.4%) dietitians working in critical care was apparent, although it should be noted that some dietitians did not work solely in the ICU setting. ICU is the one area where guidance exists for dietitians on the use of probiotics. The recent Canadian Critical Care Guidelines (2009) state that there is insufficient data to make a recommendation on the use of probiotics, prebiotics and synbiotics in the critically ill (Heyland et al., 2009). The Committee considered that the studies available are inconsistent in their method of reporting outcomes such as septic mortality, complications and diarrhoea. The variability in the probiotics used in studies and the choice of control group made the published studies difficult to assess. The probiotic prophylaxis in predicted severe acute pancreatitis (PROPTRIA) trial (Besselink et al., 2004) and concerns about risk associated with *S. boulardii* were also a cause for concern for the Committee. The American Society for Parenteral and Enteral Nutrition (ASPEN) Critical Care Guidelines of 2009 reiterate that recommendations cannot be made about the use of probiotics in the general ICU population, again due to the lack of consistent outcomes (McClave et al., 2009).

The safety issues highlighted in the literature would appear to be an aspect needing consideration. Although dietitians’ opinions about the safety of probiotics were not specifically investigated in this study, some respondents highlighted that they would not use them in specific patient groups (i.e. infants and immunocompromised, ICU
and paediatric oncology patients). Safety concerns arising from the use of probiotics were not apparent in the questionnaire responses.

The reasons quoted for not using probiotics by Dutch dietitians related to safety and functionality of the products and to products containing bacteria or "foreign" invaders (de Jong et al., 2004). In another study, nutritionists (Mc Connon et al., 2004) expressed concern about the risks associated with probiotics; however, this study focused on FF as a group of foods and did not seek specific detail on dietitians’ opinions on the safety aspects of probiotics.

3.5.7 Type of enteral feed used in CDAD

Although the majority of dietitians used a polymeric feed, there was no consistent practice in the provision of dietary fibre to patients with CDAD. A small number of studies have investigated the impact of diet on the acquisition and growth of *C. difficile*. The results of this study showed that few dietitians used elemental enteral feeds in their clinical management of CDAD patients. Elemental diet is thought to favour the growth and proliferation of *C. difficile*. An in-vitro culture study found that elemental diet enhanced the number of *C. difficile* and induced the production of *C. difficile* toxin (Iizuka et al., 2004). It has been reported that *C. difficile* toxin was frequently detected in patients undergoing elemental diet therapy who were not taking antibiotics. Faecal *C. difficile* toxin disappeared soon after the elemental diet therapy stopped (Itou et al., 1999; Itou et al., 2000). Elemental diet contains no complex carbohydrate; the absence of dietary fibre and resistant starch disturbs microbial balance in the GIT and deprives the colonic epithelium of its chief energy source and proliferation regulator. This reduces fermentation and the production of short chain fatty acids (SCFA), especially the SCFA butyrate. It has been shown that
butyrate deficiency in the colon potentiates the growth and toxin production of *C. difficile* organism (May *et al.*, 1994). It has also been suggested the relatively large amounts of amino acids in elemental diet may to provide a favourable environment for *C. difficile*. A recent review by O’Keefe (2010) stated that elemental feeding as a risk factor for *C. difficile* infection is frequently overlooked.

To provide guidance for dietitians on the provision of fibre to this patient group, the mechanisms of action of fibre in the GIT should firstly be examined. Studies that investigate the impact of fibre on the management of diarrhoea should also be reviewed, given that diarrhoea is the major symptom of CDAD. Fibre intake influences nutrient absorption, carbohydrate, fat and sterol metabolism, stool bulk and weight, colonic fermentation and gastrointestinal transit time (Kapadia *et al.*, 1995; Alam *et al.*, 1998). Fibre also improves gut barrier function, helping to prevent translocation of bacteria and toxins from the gut into the systemic circulation (Spaeth *et al.*, 1995). Fibre also promotes increased turnover or regeneration of epithelial cells (Rehman *et al.*, 2003).

The effects of supplementing enteral feeds with dietary fibre in both healthy volunteers and patients in hospital and community settings was investigated in a systematic review and meta-analysis of 51 studies (Elia *et al.*, 2008). The authors concluded that fibre supplementation was generally well tolerated. In the hospital setting, incidence of diarrhoea was reduced as the result of fibre administration (OR 0.68; 95% CI 0.48-0.96). Results showed a strong effect of fibre in reducing the incidence of diarrhoea in patient groups with a high incidence of diarrhoea and a smaller or absent effect in those with a low incidence of diarrhoea. A likely mechanism underlying the effect of fibre in reducing diarrhoea is the stimulation of
colonic water and electrolyte absorption by SCFA that are produced as a result of anaerobic metabolism of fibre. SCFA have been shown to reverse fluid secretions in the ascending colon during enteral feeding (Bowling et al., 1993). SCFA production depends on the number of types of bacteria species present in the colon, substrate source(s) and gut transit time (Wong et al., 2006), all of which have a number of properties that may be of benefit in maintaining normal bowel structure and function, and preventing or alleviating colonic based diarrhoea. SCFAs and acidic pH have been shown to contribute to resistance to *C. difficile* colonisation and proliferation in vitro (Rolfe & Iaconis, 1983; Rolfe, 1984). Different types of dietary fibre affect the type and amount of SCFA produced. Nakao et al., (2002) reported an increase in the ratio of anaerobic bacteria to aerobic bacteria with fibre supplementation. This may be beneficial as anaerobic bacteria are thought to protect against the overgrowth of potential pathogens, some of which may cause diarrhoea (Bourlioux, 1997). It is thought that lack of dietary fibre could produce an intestinal environment conducive to the growth of *C. difficile*. The recent review by O'Keefe (2010), speculates that the prolonged use of low fibre tube feeds will enhance *C. difficile* colonization and subsequent *C. difficile* associated colitis by reducing the resistance to pathogen adherence and subsequent cytotoxic injury.

3.5.8 The provision of probiotics via an enteral tube
A limitation of the present study was that the questions asked of dietitians about their use of probiotics with enteral tube feeding did not distinguish between the positions of the enteral tube. Such questions would have provided more detailed information on dietetic practice. It appears that approximately half of all dietitians either regularly or occasionally recommend probiotics via enteral feeding tubes in both CDAD and other clinical conditions. There is very little guidance from the scientific
literature or the probiotic or enteral feeding tube industries in this area. Danone Ireland Limited, the company that produce “Actimel” does not recommend the use of probiotics via enteral feeding tubes; the reason provided by the company is that clinical evidence is lacking to support its safety if used in this way, as the product is intended for oral consumption and has only been tested for oral use (Cox, M. 2010 pers. comm., 15 May 2010). Communication with representatives from Yakult, Ireland (Yakult) and Glanbia (“Everybody”) indicated that neither company had guidelines for the administration of their products via enteral feeding tubes (Jordan, D. 2011 pers. comm., 19 January; McGartland, C. 2011 pers. comm., 19 April;).

Three companies that manufacture enteral feeding tubes that are commonly used in Irish healthcare facilities were contacted to seek their position on the administration of probiotics via enteral feeding tubes. No company had recommendations; some of their comments compared the administration of probiotics to the administration of medications via enteral feeding tubes (Nolan, O. 2010, pers. comm., 4 May; Coakley, D. 2010, pers. comm., 14 May; Smith, R. 2010, pers. comm., 14 May).

The safety issues that arise with probiotics and nutrition support were addressed in a recent review by Whelan and Myers (2010). Patients receiving nutrition support are often high risk patients who are frequently critically ill and at risk of bacterial translocation or are immunocompromised and, so, have additional risk factors for probiotic infection. They are, also, regularly on medications that increase gastric pH. The method of administering nutrition support can increase patients’ risk; post-pyloric feeding enteral nutrition by-passes the gastric acid barrier completely and this can result in a greater inoculum of the probiotic surviving in the small intestine. A 10-fold increase in the dose reaching the small intestine has been reported (Whelan
Central venous catheters (CVC) are used in the administration of parenteral nutrition (PN) and these have been identified as a potential risk factor for probiotic infection (Boyle et al., 2006). The review by Whelan and Myers (2010) included 20 case reports and 52 papers with 53 trials (41 RCT’s and 12 non-randomized trials). In the case reports examined, 32 patients received various methods of nutrition support and probiotics of varying strains and doses. Bacteraemia occurred in five cases and fungaemia in 27 cases. Two patients also developed endocarditis (Land et al., 2005; Munoz et al., 2005). The risk factors were variable, but the majority of patients who developed infections had received antibiotics and had intravenous access. In eight patients, the adverse events resulted in death. The cases in which infection developed had used *L. rhamnosus* GG or *S. boulardii*. The authors commented this is probably due to these strains being used more frequently rather than them having greater virulence. The presence of a CVC also carried a greater risk; many of these patients were in ICU and required a CVC for their medical management although it was highlighted that the CVC tips were not examined for contamination. The authors of this review concluded that the risk of environmental contamination may also occur and be a greater risk factor than administration of probiotics. In the case reports of *S. boulardii* fungaemia, the patients themselves were not receiving the yeast but patients located beside them were (Cassone et al., 2003; Graf & Gavazzi, 2007).

In the 53 trials examined by Whelan and Myers (2010), the probiotics used varied and were administered in varying doses and using a range of administration methods. Subjects in the studies were from a variety of locations with a range of disorders. Many of the studies showed a reduction in mortality, sepsis or infection; in general
the studies showed either no effect or a positive effect of probiotic use on the overall outcome. Only three studies, (one post liver transplant, another in acute pancreatitis and a further study in NEC) found significant increases in negative clinical sequelae which were largely non-infectious in nature (Besselink et al., 2004; Rayes et al., 2005; Lin et al., 2008). In two of the RCT’s, there was increased negative outcome in patients in which the probiotics were administered via naso jejunal tube (NJT) (Besselink et al., 2004; Rayes et al., 2005). Whelan and Myers (2010) remark, in the three trials with negative outcomes, there are some issues with the study designs. One of the trials had low numbers which may result in statistical error (Rayes et al., 2005) and in the second trial a novel probiotic was used and the study itself has been heavily criticized (Besselink et al., 2004). In many of the studies the probiotic strains were not characterized, inconsistent doses were reported, probiotic infection occurred at different doses of probiotics, adverse events were either unreported or there was a lack of information about the adverse events. In the cases where patients died, it was difficult to attribute the patient’s death to probiotic infection.

3.5.9 CDAD and mineral and vitamin supplementation

The symptom of diarrhoea which can often be persistent and severe in CDAD can impact on the individual’s nutritional status, especially micronutrient status. There is no guidance in the literature on the provision of additional micronutrients during CDAD. From the results of this study, it can be seen that a dietitian’s decision to supplement with vitamins or minerals appears to be generally based on his/her clinical judgement. A more structured approach should be considered as mineral balance is always altered when diarrhoea persists for more than a few hours (Wiesen et al., 2006). A range of micronutrient deficiencies during diarrhoeal disease has been described; some of the micronutrient deficits identified are copper, iron,
magnesium, selenium, zinc, folate and vitamins A, B₁₂ and D (Tomkins et al., 1993). Micronutrient deficiency impairs immune function and increases susceptibility to infection (Yaqoob & Calder, 2003).

Zinc is a micronutrient that has been extensively studied for its role in diarrhoea. In the GIT, it restores mucosal barrier integrity and enterocytes, promotes brush border enzyme activity and the production of antibodies and circulating lymphocytes against intestinal pathogens (Shankar & Prasad, 1998; Hess et al., 2009; Prasad, 2009). The association between zinc and diarrhoeal associated morbidity was first noted in early observational studies that documented increased faecal zinc loss, a negative zinc balance and low tissues zinc concentration among children with diarrhoea (Anon, *Zinc and copper wastage during acute diarrhoea*, 1990). There have been a number of studies investigating prophylactic zinc supplementation and its role in diarrhoea. A recently published Cochrane review also supports the role of zinc in treating diarrhoea in children. In the 22 trials reviewed, zinc was seen to shorten the duration of an episode of diarrhoea. However, there was no benefit demonstrated in children under 6 months (Lazzerini & Ronfani, 2008). Due to the positive results of studies on zinc supplementation in children, the WHO/UNICEF now recommend zinc supplementation for the treatment of all episodes of childhood diarrhoea (WHO/UNICEF, 2004). Although there is strong evidence to support the supplementation of zinc in children, the majority of the studies on zinc supplementation have been conducted in children in developing countries and, therefore, may not be applicable to the adult population in developed countries. Nonetheless, dietitians should be more aware of zinc losses that can occur as a result
of CDAD diarrhoea. In particular, if diarrhoea is persistent, zinc supplementation should be considered, especially if nutritional intake is inadequate.

3.5.10 Limitations and future considerations
An aspect not considered in the design of this study was dietitians’ personal consumption of probiotic products. In previous studies, this has been reported to influence dietitians’ professional practice. In a study of Korean dietitians, the dietitian’s own frequency of consumption of FF had a significantly positive effect on their recommendation of such foods and those who ate FF demonstrated a more positive attitude towards the efficacy of such foods. The authors of this study expressed concern that these findings may result in some dietitians providing misleading advice to consumers, because the advice provided was not necessarily based on scientific knowledge (Cha et al., 2010). An additional factor not explored as part of this study was methods dietitians use to obtain information about probiotics. The study of Dutch dietitians showed that they got most of their information from journals, magazine articles or the internet, but would have preferred if information had been provided by independent scientists instead of through product promotions. Specific information requested was about the safety and functionality aspects of the probiotics (de Jong et al., 2004).

An important issue to be addressed from these study results is that dietetic practice in the use of probiotics is not underpinned by scientific research. Similar findings on the opinions and use of probiotics have been reported among gastroenterologists in the US. Williams et al., (2010) reported that gastroenterologists believe that there is a role for probiotics in patient care but actual practices did not concur with the published expert panel based recommendations for evidence based probiotic use.
Cha et al., (2010) commented on the need for undergraduate students of nutrition and dietetics to learn about FF from a scientific, evidence-based approach and that education about FF should be provided as continual professional development for practicing dietitians.

Given the vast amount of research into the efficacy of probiotics in different clinical conditions, the need for guidance for healthcare professionals, perhaps in the form of clinical practice guidelines should be considered. One of the most consistent findings in health service research is the gap between best practice as identified by scientific research and the actual clinical care provided (Grol & Grimshaw, 2003; Brown et al., 2004). Several studies have suggested that 10-40% of patients do not receive care that is based on current scientific evidence and that this deficit in evidence-based practice results in care that is either unnecessary or is potentially harmful in ≥20% of cases (Avezum et al., 2000; Grol & Grimshaw, 2003; Leape et al., 2003; Mc Glynn et al., 2003). A cross-sectional survey in a Swedish University Hospital explored dietitians’, occupational therapists’, and physical therapists’ attitudes towards evidence-based practice. All professions were reported to have positive attitudes towards evidence-based practice and support the use of evidence in decision making about patient care. Although the groups had good knowledge about research terminology, they lacked understanding of the specific terminology relating to evidence-based medicine. Lack of time was given as a barrier to the use of evidence-based care (Heiwe et al., 2011).
3.6 Conclusion
This is the first study to describe Irish dietitians’ opinions on, and use of, probiotics, and their current practice in the management of CDAD. The role and efficacy of probiotics in the prevention and management of CDAD is an area of emerging research and understanding. We need a greater understanding of the complex interaction between the human gastrointestinal microflora, pathogens, probiotics and antibiotics and to increase our knowledge about the role of probiotics in CDAD. The low cost, good safety profile and low risk of infection make probiotics a favourable option in the prevention and treatment of CDAD, provided sufficient evidence becomes available to support their use. Studies of appropriate statistical power and adequate follow up are necessary to provide insight into the efficacy of particular bacterial and yeast strains and the doses of these strains that are most likely to prevent CDAD and its recurrence, and treat CDAD should it develop.

The findings of this study indicate that Irish dietitians have mixed views about the role of probiotics in CDAD. Despite this, they frequently recommend probiotics in their clinical practice either orally or via enteral feeding tubes, with little standardisation of practice apparent. The probiotic strain recommended or available to prevent or treat CDAD frequently does not contain the strain for which evidence exists. Guidelines or polices in Irish healthcare facilities for probiotic use are lacking or not consistently referred to by Irish dietitians. Guidance on the use of probiotics in CDAD should be sought from current scientific literature and the development of consensus practice guidelines for dietitians managing patients with CDAD is essential.
Although the majority of Irish dietitians use a polymeric feed when enterally feeding patients with CDAD, practice on the provision of dietary fibre to this patient group is variable. The provision of additional vitamin and mineral supplementation is also dependent on the dietitian’s clinical judgement. The enteral feeding practices of Irish dietitians in this patient group need to be compliant with scientific evidence. From the review of the literature there are a number of considerations for dietetic practice. Those at high risk of developing CDAD elemental and semi elemental feeds should be avoided. A source of fibre should be provided when enterally feeding a high risk patient. In cases of CDAD where diarrhoea occurs the provision of additional vitamins and minerals should be considered to account for increased losses.

Irish dietitians in this study identified themselves as the main healthcare professional to recommend probiotics. However the survey found that there was underutilization of current scientific evidence and guidelines to conform with evidence-based practice. Health professionals need to remain competent in their knowledge of this developing area of research and be able to translate research findings into their professional practice (Schultz et al., 2011). To achieve this, it is vital that information on FF is correctly communicated to those involved in nutrition education and health promotion (Blades, 2000). Given the increasingly widespread availability and use of probiotics in both community and hospital healthcare settings, Irish dietitians need to acquire a thorough understanding of these products, including the risks and benefits of probiotic treatment and the effectiveness of probiotics using different modes of delivery. If probiotics are recommended to prevent or treat disease in patients, consideration must be given to quality control and documentation
of the efficacy of such treatment. It is imperative that dietitians develop their knowledge about probiotics so that they are able to convey science based information to their clients and healthcare professionals and their credibility as nutrition experts is strengthened (Hetherwick et al., 2006).
4.1 Conclusions and Recommendations
This study looked at a number of aspects involved in the dietetic management in patients with CDAD in Ireland. The first study’s aim was to assess the nutritional status of patients with CDAD and compare this to a group of hospital patients. The study found there was no significant difference in MUST scores between a group of patients with CDAD and a comparative hospital patient group. However the CDAD group did have a significantly lower BMI and were a significantly older. In addition, when the data from the CDAD group were compared to malnutrition data from other Irish studies, there was a higher prevalence of malnutrition (as determined by BMI) and of malnutrition risk (as determined by MUST) in the CDAD group in this study. These findings would indicate that hospitalised patients with CDAD are at high risk of malnutrition.

The second study investigated dietitians’ opinions and uses of probiotics in CDAD and other clinical conditions. It also looked at the enteral feeds being provided to these patients should tube feeding be required. This study showed that Irish dietitians have inconsistent views on the role and use of probiotics in different clinical conditions. What has emerged from the work is that probiotics are being recommended by dietitians in clinical conditions for which insufficient evidence exists, in particular patients with CDAD. It is also clear that a variety of probiotic products are being supplied within Irish health care facilities, that knowledge of the specific benefits and limitations for particular strains is poor and that very little guidance for their use exists. The study also showed that general enteral feeding practices varies among dietitians, specifically in the provision of feeds containing dietary fibre.
From the findings of this study and reviewing the literature a number of conclusions and recommendations are made:

- The dietetic profession should continue to support and be involved in the promotion, training and implementation of nutritional screening for all patient groups in both the hospital and community setting.

- Dietitians should be aware of the risk factors for the development of CDAD; in those patients at high risk who require enteral feeding the provision of feeds containing dietary fibre and the avoidance of elemental and semi elemental feeds should be considered. Supplementation of micronutrient intake including zinc in patients who develop CDAD may be beneficial. Medical and nursing staff should be aware that patients with CDAD are a patient group at high risk of malnutrition and instigate care plans that address this risk.

- Probiotics should not be recommended for use in either the prevention or treatment of CDAD, until there are further supportive trials in the area. The author is unwilling to make a recommendation endorsing any product for any patient group for the treatment or prevention of CDAD as this would contravene current evidence. The probiotic *S. bouldarii* for which there is some limited evidence is not available in Ireland. However, in countries where this product is available international guidelines do not recommend its use due to safety concerns.

- There is a need for education for practicing dietitians on the role of probiotics in clinical practice. This education should be continuous to capture the emerging evidence in the area. The information provided should be
independent of commercial influence and provide a balanced view of the scientific evidence.
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Appendix 1 – The Mini Nutritional Assessment form

![Mini Nutritional Assessment Form]

The Mini Nutritional Assessment (MNA) is a tool used to screen for malnutrition. It consists of several questions and parameters to assess the nutritional status of an individual. The form includes sections for screening, assessment, and main nutrition indicator score. The form helps in identifying individuals at risk of malnutrition and those who require further evaluation.
Appendix 2 – The Malnutrition Universal Screening Tool and supporting documents

'Malnutrition Universal Screening Tool' - MAG

'MUST' is a five-step screening tool to identify adults who are malnourished, at risk of malnutrition (undernutrition), or obese. It also includes management guidelines which can be used to develop a care plan.

It is for use in hospitals, community and other care settings and can be used by all care workers.

This guide contains:
- A flow chart showing the 5 steps to use for screening and management
- BMI chart
- Weight loss tables
- Alternative measurements when BMI cannot be obtained by measuring weight and height.

The 5 'MUST' Steps

Step 1
Measure height and weight to get a BMI score using chart provided. If unable to obtain height and weight, use the alternative procedures shown in this guide.

Step 2
Note percentage unplanned weight loss and score using tables provided.

Step 3
Estimate acute disease effect and score.

Step 4
Add scores from steps 1, 2 and 3 together to obtain overall risk of malnutrition.

Step 5
Use management guidelines and/or local policy to develop care plan.

Please refer to The ‘MUST’ Explanatory Booklet for more information when weight and height cannot be measured, and when screening patient groups in which extra care in interpretation is needed (e.g. those with fluid disturbances, plaster casts, amputations, critical illness and pregnant or lactating women). The booklet can also be used for training. See The ‘MUST’ Report for supporting evidence. Please note that ‘MUST’ has not been designed to detect deficiencies or excessive intakes of vitamins and minerals and is of use only in adults.
Step 1  +  Step 2  +  Step 3

BMI score  +  Weight loss score  +  Acute disease effect score

Step 4

Overall risk of malnutrition

Step 5

Management guidelines

0  Low Risk
Routine clinical care
• Repeat screening
  Hospital – weekly
  Care Homes – monthly
  Community – annually
  for special groups e.g., those >75 yrs

1  Medium Risk
Observe
• Document dietary intake for 3 days
• If adequate – little concern and repeat screening
  Hospital – weekly
  Care Home – at least monthly
  Community – at least every 2-3 months
• If inadequate – clinical concern – follow local policy, set goals, improve and increase overall nutritional intake, monitor and review care plan regularly

2 or more  High Risk
Treat
• Refer to dietitian, Nutritional Support Team or implement local policy
• Set goals, improve and increase overall nutritional intake
• Monitor and review care plan
  Hospital – weekly
  Care Home – monthly
  Community – monthly
• Unless detrimental or no benefit is expected from nutritional support e.g., imminent death

All risk categories:
• Treat underlying condition and provide help and advice on food choices, eating and drinking when necessary.
• Record malnutrition risk category.
• Record need for special diets and follow local policy.

Obesity:
• Record presence of obesity. For those with underlying conditions, these are generally controlled before the treatment of obesity.

Re-assess subjects identified at risk as they move through care settings

See the ‘MUST’ Explanatory booklet for further details and The ‘MUST’ Report for supporting evidence.
**Step 2 - Weight loss score**

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Alternative measurements and considerations

Step 1: BMI (body mass index)

If height cannot be measured
- Use recently documented or self-reported height (if reliable and realistic).
- If the subject does not know or is unable to report their height, use one of the alternative measurements to estimate height (ulna, knee height or demispan).

Step 2: Recent unplanned weight loss

If recent weight loss cannot be calculated, use self-reported weight loss (if reliable and realistic).

Subjective criteria

If height, weight or BMI cannot be obtained, the following criteria which relate to them can assist your professional judgement of the subject’s nutritional risk category. Please note, these criteria should be used collectively not separately as alternatives to steps 1 and 2 of ‘MUST’ and are not designed to assign a score. Mid upper arm circumference (MUAC) may be used to estimate BMI category in order to support your overall impression of the subject’s nutritional risk.

1. BMI
   - Clinical impression – thin, acceptable weight, overweight. Obvious wasting (very thin) and obesity (very overweight) can also be noted.

2. Unplanned weight loss
   - Clothes and/or jewellery have become loose fitting (weight loss).
   - History of decreased food intake, reduced appetite or swallowing problems over 3-6 months and underlying disease or psycho-social/physical disabilities likely to cause weight loss.

3. Acute disease effect
   - Acutely ill and no nutritional intake or likelihood of no intake for more than 5 days.

Further details on taking alternative measurements, special circumstances and subjective criteria can be found in The ‘MUST’ Explanatory Booklet. A copy can be downloaded at www.bapen.org.uk or purchased from the BAPEN office. The full evidence-base for ‘MUST’ is contained in The ‘MUST’ Report and is also available for purchase from the BAPEN office.

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Alternative measurements: instructions and tables

If height cannot be obtained, use length of forearm (ulna) to calculate height using tables below. (See The 'MUST' Explanatory Booklet for details of other alternative measurements (knee height and demispan) that can also be used to estimate height.)

### Estimating height from ulna length

Measure between the point of the elbow (olecranon process) and the midpoint of the prominent bone of the wrist (styloid process) (left side if possible).

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<tr>
<th>Height (ft)</th>
<th>MUAC (&lt;65 years)</th>
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<th>Height (ft)</th>
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<th>MUAC (≥65 years)</th>
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### Estimating BMI category from mid upper arm circumference (MUAC)

The subject’s left arm should be bent at the elbow at a 90 degree angle, with the upper arm held parallel to the side of the body. Measure the distance between the bony protrusion on the shoulder (acromion) and the point of the elbow (olecranon process). Mark the mid-point.

Ask the subject to let arm hang loose and measure around the upper arm at the mid-point, making sure that the tape measure is snug but not tight.

If MUAC is <23.5 cm, BMI is likely to be <20 kg/m².
If MUAC is >32.0 cm, BMI is likely to be >30 kg/m².

The use of MUAC provides a general indication of BMI and is not designed to generate an actual score for use with ‘MUST’. For further information on use of MUAC please refer to The ‘MUST’ Explanatory Booklet.
PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE:
Nutritional status of patients with Clostridium difficile-associated Diarrhoea (CDAD)

This is part of a larger study that is examining:

Immune Response and Molecular Epidemiology of Clostridium difficile-associated Diarrhoea (CDAD): A Prospective Study.

The principle investigator is: Dr Lorraine Kyne

Researcher: Yvonne Hickey

You are being invited to participate in a research study. Thank you for taking time to read this.

WHAT IS THE PURPOSE OF THIS STUDY?

*Clostridium difficile* is a bacterium, which causes diarrhoea in some patients who have taken antibiotics. Different strains of *C. difficile* diarrhoea have been responsible for major outbreaks of diarrhoeal illnesses in the UK and Canada. As part of this study we want to look at the nutritional status of patients diagnosed with *C. difficile* diarrhoea. Also to examine how *C. difficile* diarrhoea affects nutritional status of patients over a defined time period.

WHY HAVE I BEEN CHOSEN?

You have been invited to participate in this study because you are suffering from diarrhoea, caused by the *C. difficile* bacterium. We will be asking all patients with *C. difficile* diarrhoea to consider participation in the study. We hope to enrol approximately 150 patients over the next 18 months.

WHAT WILL HAPPEN IF I VOLUNTEER?

Your participation is entirely voluntary. If you initially decide to take part you can subsequently change your mind without difficulty. This will not affect your future treatment in any way. Furthermore your doctor may decide to withdraw you from this study if he or she feels it is in your best interest. If you agree to participate, you will be
requested to complete an interview. We will record information from your medical records on treatment, tests and general health. In addition, information will be gathered regarding your recent weight history and dietary intake. We will also take measurement of you weight, height, tricep skinfold thickness, upper arm and calf circumference and hand grip strength. While you are in the hospital a researcher will contact you to reassess your dietary intake and nutritional status, and will repeat the measurements that were initially taken.

ARE THERE ANY BENEFITS FROM MY PARTICIPATION?

By participating in this study you will help researchers identify the nutritional status of patient who develop C. difficile diarrhoea and how it is affected after people develop C. difficile diarrhoea.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?

We do not anticipate any discomfort or potential risks associated with participation in this study.

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

If you decide not to participate in this study your treatment will not be affected in any way.

CONFIDENTIALITY

Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to anyone.

COMPENSATION

The researchers are adequately insured by virtue of their participation in the clinical indemnity scheme.

IS THIS STUDY SAFE AND BENEFICIAL?

The St. Vincent’s Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

The main study is funded by a grant from the Health Research Board and is organised by Dr Lorraine Kyne, Consultant Geriatrician, Mater Hospital.

Research Team CONTACT PHONE: 01 716 6345

Principal investigator: Dr. Lorraine Kyne, Phone: 01 803 4242 or 01 716 6301

Consultant Physician in Medicine for the Older Person, Medicine for the Older Person Day Ward, Mater Misercordiae University Hospital.
Researcher:

Yvonne Hickey, Dietitian, St Vincent’s University Hospital

Dr. Lynda Fenelon, Consultant Microbiologist, St Vincent’s University

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

I have read and understood the Participant Information

YES ☐ NO ☐

I have had the opportunity to ask questions and discuss the study

YES ☐ NO ☐

I have received satisfactory answers to all my questions

YES ☐ NO ☐

I have received enough information about this study

YES ☐ NO ☐

I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care

YES ☐ NO ☐

I agree to take part in the study

YES ☐ NO ☐

Participant’s Signature: ____________________________ Date: __________

Participant’s Name in print: ____________________________

Witness Signature: _______________________________ Date: __________

Witness Name in print: ____________________________
Investigator’s Signature: ___________________________ Date: _________

Investigator’s Name in print: ___________________________
## Appendix 4 – Data collection record for patients with CDAD

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<td>Ulna length</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ulna length</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mid upper arm circumference</td>
<td></td>
</tr>
</tbody>
</table>
### Nutritional Intake

<table>
<thead>
<tr>
<th>Oral intake in past five days</th>
<th>Normal ↑</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than normal ↑</td>
</tr>
<tr>
<td></td>
<td>Very little / none ↑</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diet Consistency</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Consistency</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coeliac Disease</th>
<th>yes ↑</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no ↑</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral Nutritional Supplements</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes ↑</td>
<td>No ↑</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enteral feeding</th>
<th>NG NJ PEG RIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date PEG/RIG inserted</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date feeding Commenced</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed type</td>
<td></td>
</tr>
<tr>
<td>Feed Rate</td>
<td></td>
</tr>
<tr>
<td>TPN</td>
<td>Regimen details</td>
</tr>
<tr>
<td>Total volume</td>
<td></td>
</tr>
<tr>
<td>Date Commenced</td>
<td></td>
</tr>
</tbody>
</table>

| Probiotic charted on drug kardex |     |

<table>
<thead>
<tr>
<th>Previous probiotic se</th>
<th></th>
</tr>
</thead>
</table>

| Vitamin and mineral supplement |     |

188
**Step 1**  
BMI score

<table>
<thead>
<tr>
<th>BMI kg/m²</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20 (30+ Obese)</td>
<td>0</td>
</tr>
<tr>
<td>18.5-20</td>
<td>1</td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>2</td>
</tr>
</tbody>
</table>

**Step 2**  
Weight loss score

<table>
<thead>
<tr>
<th>Unplanned weight loss in past 3-6 months</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>5-10</td>
<td>1</td>
</tr>
<tr>
<td>&gt;10</td>
<td>2</td>
</tr>
</tbody>
</table>

**Step 3**  
Acute disease effect score

If patient is acutely ill and there has been or is likely to be no nutritional intake for >5 days  
Score 2

*unable to obtain height and weight.*
Appendix 5- Data collection sheet for Control group

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age</th>
<th>Sex</th>
<th>Type of ward*</th>
<th>Diagnostic Category**</th>
<th>Oedema Present?</th>
<th>Has MUST been completed?</th>
<th>If MUST was done, is their evidence of an appropriate care plan?</th>
<th>Weight (Kg)</th>
<th>Height (m) - if not available, calculate from Ulna Length</th>
<th>BMI</th>
<th>Step 1- Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>2</td>
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<td>3</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Patient Number</td>
<td>Unintentional weight loss (past 3-6 months)</td>
<td>Step 2 - Score</td>
<td>Food intake over past 5 days</td>
<td>Likely food intake over next 5 days</td>
<td>Step 3 - Score</td>
<td>MUST Score</td>
<td></td>
<td></td>
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<tr>
<td>----------------</td>
<td>--------------------------------------------</td>
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<tr>
<td>1</td>
<td>Kg</td>
<td>Normal</td>
<td>Less than normal</td>
<td>Normal</td>
<td></td>
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</tr>
</tbody>
</table>
Appendix 6 – the Health Protection Surveillance Centres infection guidelines for patients with Clostridium difficile associated disease (HPSC, 2008).

**PATIENT PLACEMENT**

Apply to all patients, residents and clients irrespective of their perceived infection risk. Include the potential for transmission of infectious agents in patient placement decisions.

Where possible, place patients who contaminate the environment or cannot maintain appropriate hygiene in single rooms.

**CONTACT PRECAUTIONS**

- Use of Frequent Hand Washing
- Personal Protective Equipment
- Personal Equipment
- Environmental Precautions

**TRANSPORT**

- Transport equipment (stretcher, bed, wheelchair) must be cleaned and disinfected before use with another patient/resident.
- Transport equipment (stretcher, bed, wheelchair) must be cleaned and disinfected before use with another patient/resident.
<table>
<thead>
<tr>
<th><strong>STANDARD PRECAUTIONS</strong></th>
<th><strong>CONTACT PRECAUTIONS</strong> (for CDAD patients in addition to Standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HAND HYGIENE</strong></td>
<td></td>
</tr>
<tr>
<td>Patients should wash their hands after toileting and before meals. HCW should provide assistance with hand washing for those patients who are unable to perform hand washing independently.</td>
<td>In addition to carrying out hand hygiene as required in Standard Precautions</td>
</tr>
<tr>
<td>Hand Hygiene is recommended:</td>
<td></td>
</tr>
<tr>
<td>• Before and after each episode of patient contact</td>
<td></td>
</tr>
<tr>
<td>• Between individual patient contacts.</td>
<td></td>
</tr>
<tr>
<td>• After contact with blood, body fluids, secretions or excretions, whether or not gloves are worn.</td>
<td></td>
</tr>
<tr>
<td>• After handling soiled/contaminated equipment, materials or the environment.</td>
<td></td>
</tr>
<tr>
<td>• Immediately after removing gloves or other protective clothing.</td>
<td></td>
</tr>
<tr>
<td>Hand may be decontaminated using both plain soap and warm water or if hands are physically clean, an alcohol based hand rub.</td>
<td></td>
</tr>
</tbody>
</table>

| **GLOVES** | |
| Should be worn as single use items. |
| Should conform to European Community Standards. |
| Gloves are recommended: |
| • For all activities that carry a risk of exposure to blood, body fluids, secretions or excretions, sharps or contaminated instruments |
| • When touching mucous membranes and non-intact skin. |
| • When handling contaminated equipment, e.g. commodes or bedpans. |
| Gloves should be: |
| • Put on immediately before an episode of patient contact, and removed as soon as the activity is completed. |
| • Changed between caring for different patients and between different care activities on the same patient. |
| • Disposed of as health care risk waste if contaminated with blood, body fluids. |

| **EYE, NASAL AND MOUTH PROTECTION** (e.g. goggles, visors and face masks) | |
| Facemasks and eye protection are recommended where there is a risk of blood, body fluids, secretions or excretions splashing into the face or eyes. |
| Masks should be single use and fluid resistant. |

| |
| None of the agents (including alcohols, chlorhexidine, iodophors or triclosan) used in antiseptic hand-wash or antiseptic hand-rub preparations are reliably sporicidal against C. difficile. The physical action of rubbing and rinsing is the only way to remove spores from hands. |

In addition to wearing gloves as required for Standard Precautions, wear gloves when entering a room for all interactions that may involve contact with the patient or potentially contaminated areas in the patients environment. |

Remove gloves: |
| • Immediately after contact with any infective material |
| • Before touching non-contaminated items and environmental surfaces |
| • Before leaving the patients environment |

Wash hands as above immediately after glove removal.
Disposable plastic aprons should be worn where there is a risk that clothing or skin may become exposed to blood, body fluids, excretions or secretions. Fluid repellent gowns may be required if there is a risk of extensive exposure to the above.

### Standard Precautions

<table>
<thead>
<tr>
<th><strong>APRONS</strong></th>
<th><strong>Patient Care Equipment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Disposable plastic aprons should be worn where there is a risk that clothing or skin may become exposed to blood, body fluids, excretions or secretions. Fluid repellent gowns may be required if there is a risk of extensive exposure to the above.</td>
<td>Handle equipment soiled with blood, body fluids, secretions and excretions in a manner that prevents skin and mucous membranes, contamination of clothing, and transfer of micro-organisms to other patients and environments. Ensure that reusable equipment is not used by another patient until it has been cleaned and reprocessed appropriately.</td>
</tr>
</tbody>
</table>

### Contact Precautions (for CDAD patients in addition to Standard)

In addition to wearing apron/gowns as required for Standard Precautions, wear aprons/gowns when entering a room for all interactions that may involve contact with the patient or potentially contaminated areas in the patients’ environment.

Remove apron/gown
- Immediately after contact with any infective material
- Before leaving the patients environment

Wash hands as above immediately after apron/gown removal.

- Dedicate medical devices (e.g., thermometers, sphygmomanometers, stethoscopes, glucose metres) to single patient use and disposable materials used whenever possible.
- Only take essential equipment and supplies into the room. Do not stockpile as unused stock will have to be discarded on cessation of Isolation Contact Precautions.
- Patient charts/records should not be taken into the room.
| STANDARD PRECAUTIONS | CONTACT PRECAUTIONS  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ENVIRONMENTAL AND EQUIPMENT DECONTAMINATION</td>
<td>(for CDAD patients in addition to Standard)</td>
</tr>
<tr>
<td>- Routine environmental cleaning is required to minimise the number of micro-organisms in the environment.</td>
<td>In addition to environmental and equipment decontamination as required for Standard Precautions:</td>
</tr>
<tr>
<td>- Particular attention should be given to frequently touched surfaces and those most likely to be contaminated with blood or body fluids e.g. bedrails, mattresses, bedside tables, commodes, doorknobs, sinks, surfaces and equipment close to the patient.</td>
<td>- Thoroughly clean the environment and all patient care equipment daily with a neutral detergent and disinfect with a sporicidal disinfectant e.g., hypochlorite solution (~1000 ppm), paying special attention to frequently touched sites and equipment close to the patient.</td>
</tr>
<tr>
<td>- Chemical disinfectants are not recommended for routine environmental cleaning.</td>
<td>- Particular attention should be given to cleaning and disinfecting immediately items likely to be faecally contaminated e.g., the under surfaces and hand contact surfaces of commodes.</td>
</tr>
<tr>
<td>- All equipment should be in a state of good repair in order to facilitate effective cleaning.</td>
<td>- Environmental faecal soiling should be cleaned and disinfected immediately.</td>
</tr>
<tr>
<td>- Place bedpan / commode utensils directly into bedpan washer-disinfector. Bedpan washers must reach a temperature of 80°C for a minimum of 1 minute. Monitor and record correct temperatures reached and the cleaning efficacy of bedpan-washers.</td>
<td>- Cutlery and crockery - No additional measures are required for cutlery and crockery washed in a dishwasher.</td>
</tr>
<tr>
<td>- All equipment should be stored dry.</td>
<td>On patient discharge/transfer cleaning and disinfection of the environment must occur upon resolution of CDAD symptoms or when a CDAD patient has their accommodation changed or is discharged from a room.</td>
</tr>
<tr>
<td>- Non-critical items such as commodes, intravenous pumps must be thoroughly cleaned prior to use on another patient/resident. If soiled with blood or body fluids, disinfect using a chlorine-releasing solution of 10000ppm, or equivalent according to manufacturers’ instructions, rinse and dry. The area should be well ventilated to avoid toxic fumes.</td>
<td>- Prior to initiating environmental cleaning and disinfection, all privacy, shower and window curtains must be removed and sent for laundering.</td>
</tr>
<tr>
<td>- When using disinfectants, staff should follow the manufacturer’s instructions for dilution and contact times.</td>
<td>- All disposable items including paper towels and toilet paper must be discarded</td>
</tr>
<tr>
<td></td>
<td>- All sterile and non-sterile supplies in the patient environment to be discarded on patient transfer/discharge.</td>
</tr>
</tbody>
</table>
**Laundry Care:**
- Laundry should be handled and transported in a manner that prevents transmission of micro-organisms to other patients, HCWs or the environment.
- Laundry should be categorised and segregated according to recommended guidelines.
- Staff handling soiled linen should wear gloves and a disposable plastic apron.
- Soiled and infectious linen should be carefully placed in an alginate stitched or water soluble bag with a tie. Then place bag into a colour-coded laundry bag which should be securely closed prior to transport to an approved laundry capable of dealing with potentially contaminated linen.
- Staff should not manually sluice or soak soiled or infected linen/clothing because of the risk of cross-infection.
- Soiled linen should be transported and stored safely.
- Linen should be heat disinfected during the wash process by raising the temperature to either 65°C for not less than 10 minutes or preferably 71°C for not less than 3 minutes.
- Disinfection of heat labile materials (according to manufacturer instructions) can be achieved at low temperatures by introducing 150 ppm of chlorine into the penultimate rinse.

**Decontamination of Medical Devices:**
- Medical devices designated as “Single Use Only” must not be reprocessed or reused under any circumstances (MDA DB 2000), (MDD) 93/42/EEC.
- Reusable medical devices should be cleaned and reprocessed according to the manufacturer’s instructions and local policy.

**Standard Precautions**
- Laundry should be handled and transported in a manner that prevents transmission of micro-organisms to other patients, HCWs or the environment.

**Contact Precautions** (for CDAD patients in addition to Standard)
- In addition to handling and transportation of laundry as required for Standard Precautions:
- All laundry should be carefully placed in an alginate stitched or water soluble bag and then placed into a laundry bag clearly identified with labels, colour-coding or other methods prior to transport to an approved laundry capable of dealing with contaminated linen.

This symbol means “Single Use Only” (BS EN 980:1997).
MANAGEMENT OF HEALTH CARE RISK WASTE:

Dispose of healthcare risk waste in accordance with the Department of Health & Children's National Guidelines for Waste Disposal, which outlines the categorisation and segregation of healthcare waste.

DISPOSAL OF SHARPS:
- Syringes and needles should be disposed of as a single unit.
- Used sharps should be carefully discarded into designated sharps containers at the point of use.
- Needles should not be re-capped, bent, broken or disassembled.
- Sharps should not be passed from person to person by hand.
- Guidelines should be available at local level on the management of needle stick and sharps injuries.

CONTACT PRECAUTIONS (for CDAD patients in addition to Standard)

Waste contaminated with diarrhoea from a suspected or known CDAD patient should be disposed as healthcare risk waste within a healthcare facility.

No additional precautions are needed for non-healthcare waste that is being removed from rooms of patients on Contact Precautions.
Spillages of blood, urine, faeces or vomit should be dealt with immediately wearing protective clothing (i.e. disposable gloves and apron).

For spillages of body fluid (e.g., urine, faeces or vomit), soak up as much of the visible material as possible with disposable paper towels. Dispose of the soiled paper towels according to national guidelines.

Clean the area using warm water and general purpose neutral detergent. Disinfect using a chlorine-releasing solution of 1000ppm, or equivalent according to manufacturers' instructions, rinse and dry.

Discard gloves and apron according to national guidelines. Wash and dry hands thoroughly.

Do not apply chlorine-based disinfectants directly onto spillages of urine as it may result in the release of chlorine vapour.

For blood spillages: Decontaminate all blood spills with a chlorine-based disinfectant (e.g., powder, granules or liquid containing 10,000ppm available chlorine) or suitable alternative, in line with the manufacturer’s instructions and local policy.

Wipe up the spillage with disposable paper towels and discard into a yellow plastic bag. Wash the area with a general purpose detergent and water.

Inspect items contaminated with blood or body fluids: following decontamination and disinfection using a chlorine-releasing solution of 1000ppm, or equivalent according to manufacturers' instructions, rinse and dry.
Appendix 7 – St Vincent’s University Hospital Infection Control guidelines for *Clostridium difficile* associated disease.

St Vincent’s Healthcare Group

10. INFECTIOUS DISEASES

10.1. Overview of Infection Control Management of Infectious Diseases

The infection prevention and control (IPC) team should be informed promptly if any patient known or suspected to have any of the following infections is admitted (ext 4948/4088, bleep 122).

Duration of isolation varies according to the infection with which the patient had been diagnosed. Some infections require that the patient be isolated for the entirety of their hospital stay; with other infections, the patient may be removed from isolation once they have been symptom-free for a specified time period, or have had appropriate treatment for a specified time. Further information on some infections may be found further on in this section; otherwise, please discuss with the IPC team.

Recommendations may be subject to change following assessment by the IPC team.

For the management of patients in isolation, please refer to Guidelines on management of patients in isolation (Section 30).

<table>
<thead>
<tr>
<th>Notifiable Disease</th>
<th>Infective material</th>
<th>Additional Precautions</th>
<th>Isolation required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
<td>Feces</td>
<td>Contact</td>
<td>Single room</td>
</tr>
<tr>
<td>Chickenpox (Varicella zoster virus)</td>
<td>No</td>
<td>Respiratory secretions Lesion secretions</td>
<td>Airborne Contact</td>
</tr>
<tr>
<td>Cholera</td>
<td>Feces</td>
<td>Contact</td>
<td>Not required</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>No</td>
<td>Feces Faecally contaminated objects and surfaces</td>
<td>Contact</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease (CJD)</td>
<td>Yes</td>
<td>Brain, spinal, cranial and dura mater Optic nerve and retina</td>
<td>Seek advice from Infection control</td>
</tr>
<tr>
<td>Variant CJD (vCJD)</td>
<td>Yes</td>
<td>As above and lymphoid tissue</td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Yes</td>
<td>Oral &amp; nasal discharges</td>
<td>Droplet</td>
</tr>
<tr>
<td>E coli O157</td>
<td>Yes</td>
<td>Feces</td>
<td>Contact</td>
</tr>
<tr>
<td>Hemophilus influenza B (invasive)</td>
<td>Yes</td>
<td>Respiratory secretions</td>
<td>Droplet</td>
</tr>
</tbody>
</table>
St Vincent’s Healthcare Group

10.5. **Clostridium difficile**

This is a **NOTIFIABLE DISEASE**

**AGENT:** Clostridium difficile

**INCUBATION PERIOD:** Variable

**TRANSMISSION:** Environmental contamination
Hands of healthcare workers
Faecal-oral.

**PREDISPOSING FACTORS:** Antibiotic therapy, especially cephalosporins, clindamycin and quinolones (e.g., ciprofloxacin)
Exposure to infected patients

**INFECTIVE MATERIAL:** Faeces
Faecally contaminated objects/surfaces

**DURATION OF INFECTIVITY:** While symptomatic, and until free of symptoms for 72 hours

**PRECAUTIONS:** **CONTACT PRECAUTIONS**
Isolation of the patient in a single room until free of symptoms for 72 hours.
In the event of non-availability of a single room, cohorting of patients with *C. difficile* may have to be considered
A commode should be secured for the sole use of the infected patient.
Environmental cleaning with 1,000ppm hypochlorite.

**TREATMENT:** Discontinue antibiotic therapy if clinically feasible.
Do not use anti-diarrhoeal agents
Metronidazole or vancomycin orally, depending on clinical severity

**PERIOD OF ISOLATION:** From onset of symptoms, until symptom free for 72 hours
Questionnaire - Dietetic practice in Ireland - The use of probiotics and enteral feeding in patients with Clostridium difficile associated diarrhoea

Dear Member

I am a dietitian working in St Vincent’s University Hospital and am currently completing a Masters degree with the School of Biological Sciences, Dublin Institute of Technology under the supervision of Dr. Clare Corish.

My primary area of research is an investigation of the nutritional status of patients who develop Clostridium difficile infection in hospital. However, in recent years, a number of studies have been published on the use of probiotics as an emerging therapy in both the prevention of Clostridium difficile (Hickson et al. 2007) and the treatment of patients who develop this infection (Mc Farland, 2006). I now wish to investigate the current use of probiotics in dietetic practice focusing on patients with Clostridium difficile. In addition I would also like to ascertain Dietitians’/ INDI members’ opinions regarding the use of probiotics in the management of Clostridium difficile and other medical conditions.

To obtain this information, I am circulating this questionnaire to all members of the INDI. The questionnaire will collect some demographic data on respondents (e.g. place and area of work, years practicing), and information on the use and administration of probiotics in patients with Clostridium difficile associated diarrhoea. The questionnaire will also include questions relating to the dietetic management of enterally fed patients who develop Clostridium difficile associated diarrhoea.

The questionnaire is divided into 4 sections and will take approximately 5 minutes to complete. Please complete each section providing me with your opinions and current practices and return in the included stamped addressed envelope by the 31st of March 2010.

All completed questionnaires will be entered into a draw to win a € 75 One 4all gift voucher in appreciation of your help and time with this

If you have any queries, please do not hesitate to contact me.

Yvonne Hickey y.hickey@st-vincents.ie
**Section 1 - Baseline Details**

(a) Gender

- Male [ ]
- Female [ ]

(b) Place of employment

- Hospital [ ]
  - Please name hospital: ____________________________
- Community dietetics [ ]
  - Please name HSE area: ____________________________
- Private practice [ ]
- Student [ ]
- Other [ ]
  - Please state: ____________________________________

(c) How many whole time equivalent (WTE) dietitians work in your department?

_________________________________________

(d) How many years have you been working as a qualified dietitian?

- Less than one year [ ]
- 1-5 years [ ]
- 6-15 years [ ]
- 16-25 years [ ]
- + 25 years [ ]

(e) Which best describes the patients you work with?

- Paediatrics [ ]
- Adults [ ]

(f) What areas of dietetic practice do you currently work in (e.g. care of the elderly, surgery, gastroenterology, etc....)

___________________________________________________________________________

**Section 2 – Your Opinions**

(a) Do you think probiotics have a place in dietetic practice in the prevention of Clostridium difficile?

- Yes [ ]
- No [ ]
- Don’t know [ ]

Please give a reason for your answer: ____________________________________________
(b) Do you think probiotics have a place in dietetic practice in the treatment of Clostridium difficile?

Yes ☐ No ☐ Don’t know ☐

Please give a reason for your answer: ________________________________________________________________

______________________________________________________________________________

(c) Would you recommend the use of probiotics in your clinical practice in any of the following clinical conditions?

I do not recommend the use of probiotics ☐

OR

Liver disease ☐
Inflammatory bowel disease ☐
Irritable bowel syndrome ☐
Small bowel bacterial overgrowth ☐
Acute gastroenteritis ☐
Necrotising enterocolitis ☐

Other conditions:
______________________________________________________________
________________________________________________________________

Section 3 - Probiotics in practice

(a) Does your hospital/place of work have a policy/guidelines for the use of probiotics?

Yes ☐ No ☐

(b) Does your hospital/place of work have a policy/guidelines for the use of probiotics specifically in patients with Clostridium difficile associated diarrhoea?

Yes ☐ No ☐

(c) Does your hospital/place of work use/supply probiotics to patients?

Yes ☐ No ☐
(d) Do you use probiotics in the prevention of Clostridium difficile associated diarrhoea in at risk patients?
   Yes ☐ No ☐ Occasionally ☐

(e) Do you use probiotics used in the treatment of Clostridium difficile associated diarrhoea?
   Yes ☐ No ☐ Occasionally ☐

(f) If probiotics are commenced in patients with Clostridium difficile associated diarrhoea, who generally recommends their commencement? (Choose more than one option if appropriate)
   Not applicable ☐ Microbiologist ☐
   Dietitian/clinical nutritionist ☐ Nursing Staff ☐
   Medical staff ☐ Pharmacist ☐
   Other ____________________

(g) If probiotics are commenced, who recommends their commencement most often? (Please classify 1-4, 1 being the most often, 4 not as often)
   Not applicable ☐
   1. ____________________ 2. ____________________
   3. ____________________ 4. ____________________

(h) In what form are the probiotics given?
   Yogurts containing probiotics ☐ Tablet / Capsule ☐
   Yogurt drinks containing probiotics ☐

(i) What different brand(s) of products are used (please specify product and type e.g. yogurt and brand)
   __________________________________________________________________________
   __________________________________________________________________________

(j) If probiotics are used, what strain(s) of probiotic is used?
   Unknown ☐
   Strain(s):___________________________________________________________________
   __________________________________________________________________________
(k) If probiotics are used, what determines the strain of probiotic or brand of products used in patients with Clostridium difficile associated diarrhoea? (More than one option can be chosen)

- The clinical evidence
- The product supplied by catering
- The product supplied by pharmacy
- Hospital guidelines
- Medical/ Microbiological opinions
- Other:_____________________________________

(l) Do you recommend administration of probiotics to patients who develop diarrhoea? If the diarrhoea is not caused by Clostridium difficile and who are on antibiotics?

- Yes   ☐  No ☐ Occasionally ☐

(m) Do you recommend administration of probiotics to patients who develop diarrhoea? If the diarrhoea is not caused by Clostridium difficile and is of unknown origin?

- Yes ☐ No ☐ Occasionally ☐

(n) Would you recommend the commencement of a multivitamin or mineral supplement in a patient who is Clostridium difficile positive? (more than one option can be chosen)

- Yes, always ☐ Would depend on patient’s diagnosis ☐
- Would depend on patient’s nutritional status ☐
- Other reason: ____________________________________________________________

Section 4– Enteral feeding

(a) Do you recommend administration of probiotics via enteral tubes if a patient being tube fed gets Clostridium difficile associated diarrhoea?

- Yes ☐ No ☐ Occasionally ☐ Not applicable ☐

(b) Do you recommend administration of probiotics via enteral tubes to patients with other clinical conditions?

- Yes ☐ No ☐ Occasionally ☐ Not applicable ☐
(c) If a tube fed patient develops Clostridium difficile what type of feed would you use most often?

- Fibre containing
- Non fibre containing
- A mixture of fibre and non fibre containing
- Parenteral nutrition is commenced

Please provide any further comments you may have on the use of probiotics and/or nutritional management in patients with Clostridium difficile associated diarrhoea?

___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________

Thank you for taking the time to complete this questionnaire.

Your response and time is greatly appreciated.

Please return in included envelope

Yvonne Hickey, Dietitian
Appendix 9 – Irish Hospitals represented by responses from dietitians.

Hospital
Adelaide and Meath Hospital Incorporating The National Childrens Hospital
Beaumont Hospital
Bons Secours Cork
Bons Secours Dublin
Cavan General Hospital
Connolly Hospital Blanchardstown
Cork University Hospital
Kerry General Hospital
Letterkenny General Hospital
Mary’s Hospital Phoenix Park
Mater Misericordiae University Hospital
Mater Private Hospital
Mayo General Hospital
Mercy University Hospital Cork
Merlin Park University Hospital Galway
Mid Western Regional Hospital Dooradoyle
Midland Regional Hospital Mullingar
Midland Regional Hospital Portlaoise
Midland Regional Hospital Tullamore
Monaghan General Hospital
Mount Carmel Hospital
Mount Carmel Hospital
Naas General Hospital
Our Lady’s of Lourdes Hospital Drogheda
Our Ladys Children Hospital Crumlin
Portiuncula Hospital
Roscommon County Hospital
Sligo General Hospital
South Infirmary Victoria University Hospital Cork
South Tipperary General Hospital
St Columcille’s Hospital
St Finbarrs Hospital, Cork
St James Hospital
St Lukes Hospital Rathgar
St Lukes Kilkenny
St Michaels Hospital Dun Laoghaire
St Vincent’s Private Hospital
St Vincent’s University Hospital
Temple Street Childrens University Hospital
The National Maternity Hospital
University Hospital Galway
UPMC Beacon Hospital
Waterford Regional Hospital
<table>
<thead>
<tr>
<th>Product name and manufacturer</th>
<th>Probiotic Genus, species, strain (commercial strain designation) in the product</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everybody Yoplait</td>
<td><em>Lactobacillus rhamnosus GG</em></td>
<td>Yogurt drink</td>
</tr>
<tr>
<td>Actimel Danone</td>
<td><em>Lactobacillus bulgaricus</em>, <em>Streptococcus thermophilus</em>, <em>Lactobacillus casei Imunitas (DN114001)</em></td>
<td>Yogurt drink</td>
</tr>
<tr>
<td>Yakult Yakult</td>
<td><em>Lactobacillus casei ShirotA</em></td>
<td>Yogurt drink</td>
</tr>
<tr>
<td>Udos Super 8</td>
<td><em>Lactobacillus acidophilus</em>, <em>Lactobacillus rhamnosus</em>, <em>Streptococcus thermophilus</em>, <em>Lactobacillus plantarum</em>, <em>Bifidobacterium bifidum</em>, <em>Bifidobacterium longum</em>, <em>Lactobacillus bulgaricus</em>, <em>Lactobacillus salivarius</em></td>
<td>Capsules</td>
</tr>
<tr>
<td>Acidophilus Complete Sona</td>
<td><em>Lactobacillus Lactis</em>, <em>Lactobacillus Acidophilus</em>, <em>Lactobacillus Para Casei</em></td>
<td>Capsules</td>
</tr>
<tr>
<td>VSL # 3 Living Shield</td>
<td><em>Streptococcus thermophilus</em>, <em>Bifidobacterium breve</em>, <em>Bifidobacterium longum</em>, <em>Bifidobacterium infantis</em>, <em>Lactobacillus acidophilus</em>, <em>Lactobacillus plantus</em>, <em>Lactobacillus paracasei</em>, <em>Lactobacillus bulgaricus</em></td>
<td>Sachet, To be added to water</td>
</tr>
<tr>
<td>Old Mac Donnells Farm Natural Yoghurt Old Mac Donnells Farm</td>
<td><em>Lactobacillus bulgaricus</em>, <em>Streptococcus thermophilus</em>, <em>Bifidobacterium longum</em>, <em>Lactobacillus acidophilus</em></td>
<td>Yogurt</td>
</tr>
<tr>
<td>Activa Danone</td>
<td><em>Lactobacillus bulgaricus</em>, <em>Streptococcus thermophilus</em>, <em>Bifidobacterium Acti Regularis</em></td>
<td>Yogurt</td>
</tr>
<tr>
<td>Mixed seeds yogurt Yoplait</td>
<td><em>Bifidobacterium BB12 r</em></td>
<td>Yogurt</td>
</tr>
<tr>
<td>Product name and manufacturer</td>
<td>Probiotic Genus, species, strain (commercial strain designation) in the product</td>
<td>Form</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>------</td>
</tr>
</tbody>
</table>
| Yogurt Glenisk Adults products | Active cultures – *Streptococcus thermophilus*, *Lactobacillus bulgaricus*  
Probiotic cultures – *Lactobacillus casei*, *Bifidus*  
Childrens products *Lactobacillus casei* | Yogurt |
| Restore Protexin Lactobacillus casei  
Lactobacillus rhamnosus  
*Streptococcus thermophilus*  
*Bifidobacterium breve*  
*Lactobacillus acidophilus*  
*Bifidobacterium infantis*  
*Lactobacillus bulgaricus* | Sachet added to fluid |
Publications and Presentations

Publication


Poster Presentations

Irish Dietitians' opinions and use of probiotics in *Clostridium difficile* - associated disease. **Dublin Institute of Technology Annual Graduate Research Symposium, Institute of Technology Kevin Street, Dublin, 28 January 2011.**


Irish Dietitians' opinions and use of probiotics in *Clostridium difficile* - associated disease. **Irish Nutrition and Dietetic Institute Research Study Afternoon, Dublin, 8 October 2011.**
The prevalence of malnutrition in patients who develop *Clostridium difficile* - associated disease. Dublin Institute of Technology Annual Graduate Research Symposium, Dublin Institute of Technology Aungier Street, Dublin, 2 November 2011.